FORMULATION AND EVALUATION OF FLOATING MICROPARTICLES OF CLARITHROMYCIN

Dissertation

Submitted to

The Tamil Nadu Dr. M.G. R. Medical University, Chennai.

In partial fulfillment for the award of the degree of

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In

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By

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OCTOBER 2013

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CERTIFICATE

This is to certify that, this thesis work entitled "**FORMULATION AND EVALUATION OF FLOATING MICROPARTICLES OF CLARITHROMYCIN"** submitted in partial fulfillment of the requirements for the award of degree of Master of Pharmacy in Pharmaceutics of The Tamil Nadu Dr. M.G.R Medical University, Chennai is a bonafide work carried out by **Reg.No:26113310** and was guided and supervised by me during the academic year Nov2012-Oct 2013.

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EXAMINERS:

1.

2.

PLACE: MADURAI

DATE:

DECLARATION

I hereby declare that this thesis work entitled **"FORMULATION AND EVALUATION OF FLOATING MICROPARTICLES OF CLARITHROMYCIN"** submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai was carried out by me in the Department of Pharmaceutics, Ultra College of Pharmacy, Madurai under the valuable and efficient guidance of **Dr.C.VIJAYA M.Pharm Ph.D,** Department of pharmaceutics, Ultra College of Pharmacy, Madurai during the academic year Nov 2012-Oct 2013. I also declare that the matter embodied in it is a genuine work and the same has not to formed the basis for the award of any degree, diploma, associate ship, fellowship of any other university or institution.

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Acknowledgement

The joyness, satisfaction and euphoria that come along with successful completion of any work would be incomplete unless we mention the people who made it possible whose constant guidance and encouragement served as a beam of light and crowed out efforts.

A sense of triumph is very much justified at this stage of completion of my dissertation. It is a pleasure to utilize this opportunity of acknowledging all those people who have helped me to complete my dissertation.

It is immense pleasure that I take this opportunity to express my heartful thanks and I Dedicate this dissertation work to my parents ***Gopalakrishnan and Latha*** *for their Invincible love, spiritual blessings, illimitable sacrifices and their continous ssupport and motivation throughout my project*

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ABBREVIATIONS

S.No	Abbreviation	Remarks
1	^{0}C	Degree Celsius
2	$t^{1/2}$	Half life
3	hrs	Hours
4	Fig	Figure
5	µg/ml	Microgram per milliliter
6	SR	Sustain release
7	SEM	Scanning electron microscopy
8	rpm	Revolutions per minute
9	SD	Standard Deviation
10	wt	Weight
11	mg	Milligram
12	ml	Millilitre
13	mm	Millimeter
14	nm	Nanometer
15	w/v	Weight by volume
16	%	Percentage
17	e.g.	Example
18	λ max	Maximum absorbance
19	CRDDS	Controlled release drug delivery system
20	EC	Ethyl cellulose
21	GET	Gastric emptying time
22	GIT	Gastrointestinal track
23	GRDDS	Gastroretentive drug delivery system
24	GRT	Gastric retention time
25	HCl Hydrochloric acid	
26	KBr	Potassium bromide
27	Min	Minute
28	R	Correlation coefficient
29	SL.No	Serial number
30	UV	Ultraviolet

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INTRODUCTION

Recentlyin the field of pharmaceutical technology great efforts are being directed towards the refabrication of existing drug molecules in a fashion, capable of solving problem related to poor water solubility, poor bioavailability, dosing problem, stability, toxicity, etc. This trend of working has led to development of new drug delivery systems.

Even today, conventional drug delivery systems are primary pharmaceutical products commonly seen in prescriptions and 'over the counter' market place. They provide prompt release of the drug but in order to achieve as well as maintain drug concentration within therapeuticallyachieved range,itisoften necessary to administer it several times a day. Conventional drug therapy results in significant fluctuations of drug concentration in systemic circulation causing either lethal effect

or no therapeutic action.[1]

Basic goal of drug therapy is to provide therapeutic amount of drug to proper site in body to promptly achieve and then maintain desired drug concentration. This idealized objective points to two aspects most important to the drug delivery, namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to specific organ or tissue while temporal delivery refers to controlling rate of drug delivery to that specific organ or tissue.[2]

Despite tremendousadvancement in drug delivery, oral route remains preferred route for administration.[3] Oral controlled release dosage forms have been developed over past three decades. These drug delivery system have a great potential of solving problems associated with conventional multiple dosing system like strict adherence to timely dosing, flip flop plasma concentration, associated side effects due to systemic accumulation of drug. Thus, there are numerous advantages such asimproved efficacy, reduced toxicity, improved patient compliance and convenience, reduction in health care cost, etc.[4] However, this approach is bedilled with several physiological difficulties such as inability to restrain and locate controlled drug delivery system within the desired region of GIT, due to variable gastric emptying and motility. Furthermore the relative brief gastric emptying time in humans which normally averages 2-3 hrs through major absorption zone i.e. stomach and upper part of intestine can result in incomplete drug release from drug delivery system leading to low bioavailability and thus reduced efficacy of administered dose.[5]

Efforts to improve oral drug bioavailability have grown in parallel withpharmaceutical industry. As the number and chemical diversity of drugs has increased, new strategies are required to develop orally active therapeutics. The past two decades have been characterised by an increased understanding of causes of low bioavailability and great deal of innovation in oral delivery technologies, marked by an unprecedented growth of drug delivery industry.[6]

It is evident from the recent scientific and patent literature that an increasedinterest in novel dosage forms that are retained in stomach for prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in GIT is to control gastric residence time.[7]

Control of placement of drug delivery system in specific region of GIT offersadvantage for variety of important drugs characterized by narrow absorption window in GIT or drugs with stability problem. These considerations have led to development of unique oral controlled release dosage form with gastro retentive properties i.e. dosage form could be retained in the stomach for several hours andrelease the drug there in a controlled and prolonged manner, so that drug could be supplied continuously to its absorption site in the upper GIT.[5]

To comprehend the considerations taken in design of gastro retentive dosage forms and to evaluate their performance, the relevant anatomy and physiology of GIT must be fully understood.[8]

The GIT is essentially a tube about 9 m long that runs through middle ofbody from mouth to anus and include throat(pharynx), oesophagus, stomach, small intestine(consisting of duodenum, jejunum and ileum) and large intestine(consisting of cecum, appendix, colon and retum). In the living person it is shorter because the muscles along walls of GIT organs are in state of tone (sustained contraction). Wavelike contractions of smooth muscle in wall of GIT propel the food along the tract from oesophagus to anus.[9]

Stomach: An overview

The stomach is J shaped enlargement of GIT directly inferior to diaphragm in epigastric, umbilical and left hypochondriac regions of abdomen. It connects oesophagus to duodenum, first part of small intestine and provides a barrier to delivery of drugs to small intestine. Its size varies according to amount of distention: up to 1500 ml following a meal; after food has emptied, a collapsed state is obtained with resting volume of only 25-50 ml.

Anatomy of stomach

The stomach has four regions:

- Cardia
  .
- Fundus.
- Body
- Pylorus.

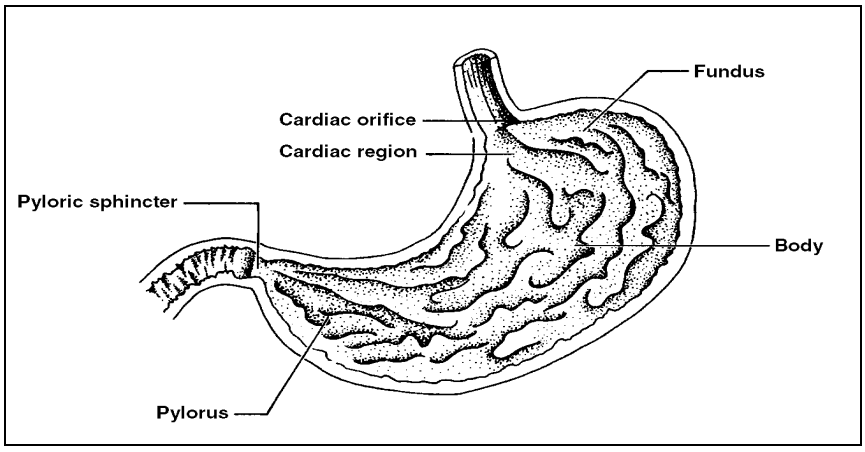


Fig No.1: Anatomy of Stomach

Cardia surrounds superior opening of stomach. The rounded portion superior to and to the left of cardia is **fundus**. Inferior to fundus is large central portion of stomach called **body**. The region of stomach that connects to duodenum, is **pylorus**. It has two parts pyloric antrum, which connects to the body of stomach and pyloric canal which leads to duodenum. The pylorus communicates with duodenum of small intestine via sphincter called pyloric spincter.

The main function of the fundus and body is storage, whereas that of cardia is mixingor grinding. The fundus adjusts the increased volume during eating by relaxation of the fundus muscle fibres. The fundus also exerts a steady pressure on the gastric contents pressing them towards the distal region. The pyloric sphincter has diameter of 12.867 mm in humans and act as sieve as well as mechanical stricture to passage of large particles. Antrum does grinding.

Histology of stomach

The stomach wall is composed of the four basic layers. Simple columnar epithelial cells line the entire mucosal surface of the stomach. Epithelial cells extend down into the lamina propria, where they form columns of secretary cells calledgastric glands. The gastric glands contain three types of exocrine gland cells that secrete their products into the stomach lumen.

- Mucous neck cells.
- Chief cell.
- Parietal cells.

The chief cells secrete pepsinogen and gastric lipase. Parietal cells produce hydrochloric acid and intrinsic factor. Both mucosal surface cells and mucous neck cells secrete mucus and bicarbonate. They protect the stomach from adverse effects of hydrochloric acid as mucosa has a lubricating effect, it allow chyme to move freely through the digestive system.

Functions of stomach

The stomach carries out three major functions. It stores food, digests food and delivers food to the small intestine at a rate that the small intestine can handle.

- Mixes saliva, food, and gastric juice to form chyme.
- It acts as a reservoir for holding food before release into the small intestine.
- Secretes gastric juice, which contains hydrochloric acid, pepsin, intrinsic factor and gastric lipase.
- Secrete gastrin into the blood.

Physiology of stomach

Various factors like the absorption ability, presystemic clearance, gastric motility,

gastrointestinal transit time and gastrointestinal emptying time will have an influence on the bioavailability of drug from the dosage form.

Absorption ability

The absorption capability of various segments of gastrointestinal tract differs from each other i.e. most of the absorption takes place in small intestine and lesserextent in stomach and colon. Unless drugs are absorbed equally in small intestine and colon, the duration for most of the drugs is 3-8 hours. This is the major limiting factor for sustained release and controlled release drug delivery systems.

Presystemic clearance

Even if drugs are absorbed equally well throughout the gastrointestinal tract, bioavailability is significantly reduced by the site-specific changes in presystemic clearance. Degradation of the drug is also carried out by hydrolysis in the stomach, enzymatic digestion and metabolism in the brush border of the gut wall and by the microorganisms. Such degradation may lead to high variation in the plasma drug concentration and poor absorption of drug into systemic circulation.

Gastric emptying

The total transit time of foods and dosage forms in human from stomach to ileocecal junction is approximately 3 to 6 hr and 6 to 10 hr in fasted and fed states respectively. Process of gastric emptying occurs in both during fed and fasted states. However, the pattern of motility differs markedly in the two states.

In fasted state, it is characterized by interdigestive cycle both through stomach and small intestine, every 2-3 hrs. This activity is called interdigestive myoelectric cycle or migrating myoelectric complex. Each cycle lasts 90-120 minutes and is composed of four phases[12].

Phase I lasts 40-60 minutes, in which contraction are at minimum, there is little or no movement of liquid or solids through intestine.

Phase II with a length of 20-40 minutes has intermediate amplitude contraction and involves bile secretions.

Phase III is also termed 'housekeeper waves' and extends for 10-20 minutes. It is initiated in thestomach in most cases or in the duodenum, with very high amplitude contraction, with a frequency of 4-5 Hz per minute and maximal pyloric opening, characterizing this phase, which enables efficient evacuation of stomach contents. The segregation of liquid and solid occurs, liquid tend to migrate during phase II and solid during phase III.

Phase IV is brief transitional phase that occurs between phase II and phase III. Phase IV has a length of less than 5 minutes and connects the maximal amplitude contractions to the basal phase. In the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. In other words, feeding results in a lag time prior to the onset of gastric emptying.

The digestive or fed state is observed in response to meal ingestion. It resembles fasting phase II and is not cyclical, but continuous, provided that the food remains in the stomach. It is thought that the sieving efficiency (i.e. ability of stomach to grind food into smaller size) of the stomach is enhanced by fed pattern or by the presence of food. Patterns of contractions in the stomach occur such that solid food is reduced to particles of less than 1 mm diameter that are emptied through pylorus as
suspension.

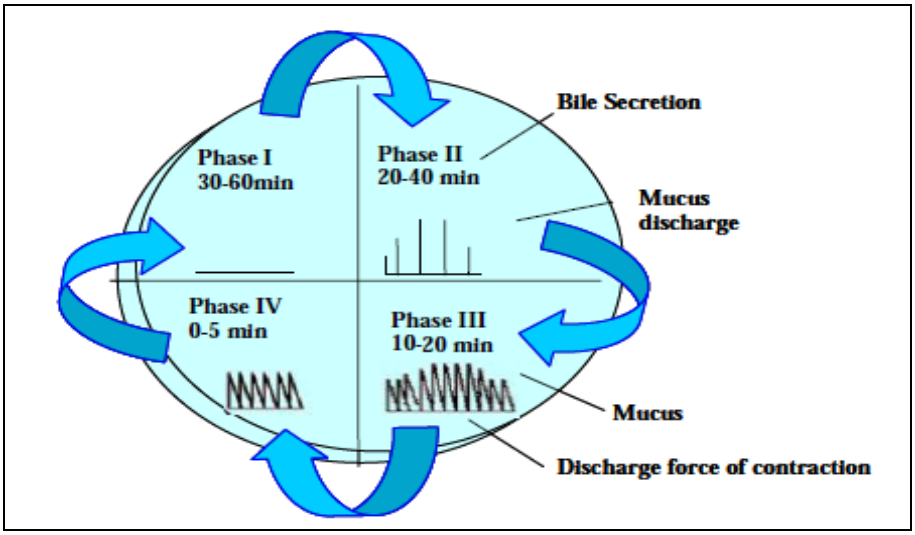


Fig No. 2: Schematic representation of interdigestive motility pattern

Table No. 1: Salient Features Of Upper Gastrointestinal Tract

Section	Length (m)	Transit time (h)	pH	Microbial count	Absorbing surface area (m_2)	Absorption pathway
Stomach	0.2	Variable	1-4	<103	0.1	P, C, A
Small Intestine	6-10	3 ± 1	5-7.5	103 – 1010	120-200	P, C, A, F, I, E, CM

P – Passive diffusion C – Aqueous channel transport

A – Active transport F – Facilitated transport

I – Ion-pair transport E – Entero-or pinocytosis

CM – Carrier mediated transport

Since most of the drugs are absorbed from the upper part of intestine, the total effective time for the drug absorption is 3-8 hours. So one has to take most of the drugs 3-6 times a day.

Regulation of gastric secretion

Both neural and hormonal mechanisms control the secretion of gastric juice and the contraction of smooth muscles in the stomach wall. Events in gastric secretion occur in three overlapping phases: cephalic phase, gastric phase and intestinal phase.

1. Cephalic phase

The cephalic phase refers to the influence of the brain on secretion. Even before food enters the stomach, the sight, taste or thought of food initiate this phase, the secretion is brought about through stimulation of the nerve. This leads to presence of acid and pepsin in the stomach even before food enters the stomach.

2. *Gastric phase*

The gastric phase of secretions is brought about by the presence of food in the stomach. It is controlled by the hormone gastrin, which is produced in the mucosa of

pyloric region of stomach. Gastrin is released in response to stretching of the antrum caused by the presence of food in this region or in response to specific substance in food; particularly proteins, alcohol and coffee are also potent stimulants of gastrin release. Once released, the gastrin is transported through the blood to stomach where it stimulates the secretion of hydrochloric acid and pepsinogen.

3. Intestinal phase

The intestinal phase of acid secretion refers to the influence of the small intestine on gastric secretion. If the material present in the duodenum of the small intestine is too acidic, a hormone is released by the intestinal mucosa. This hormone is carried by blood to the body of the stomach where it inhibits further acid secretion. This serves as a protective device for the small intestine, which is not well protected against acid as the stomach. The total volume of gastric secretion in response to all the stimuli mentioned above is approximately 2-3 liters per day.

Factors Affecting Gastric Retention

1. **Density:** GRT is a function of dosage form buoyancy that is dependent on the density. Density of the dosage form should be less than the gastric contents (1.004gm/ml).
2. **Size:** Dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm.
3. **Shape of dosage form:** Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT @ 90% to 100% retention at 24 hours compared with other shapes.
4. **Single or multiple unit formulation:** Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles orcontaining incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
5. **Fed or unfed state:** Under fasting conditions, GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

6. **Nature of meal:** feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
7. **Caloric content:** GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.
8. **Frequency of feed:** the GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.
9. **Gender:** Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
10. **Age:** Elderly people, especially those over 70 years, have a significantly longerGRT.
11. **Posture:** GRT can vary between supine and upright ambulatory states of the patients.
12. **Concomitant drug administration:** Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride[13]

Timmermans et al studied the effect of buoyancy, posture, and nature of meals on the gastric emptying process *In vivo* using gamma scintigraphy. To perform these studies, floating and nonfloating capsules of 3 different sizes having a diameter of 4.8 mm(small units), 7.5mm(medium units), and 9.9 mm (large units), were formulated[14]. On comparison of floating and nonfloating dosage units, it was concluded that regardless of their sizes the floating dosage units remained buoyant on the gastric contents throughout their residence in the gastrointestinal tract, while the non floating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastroduodenal junction were protected from the peristaltic waves during digestive phase while the non floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase (Figure 3). It was also observed that of the floating and non floating units, the floating units were had a longer gastric residence time for small and medium units while no significant difference was seen between the two types of large unit dosage forms.[15]

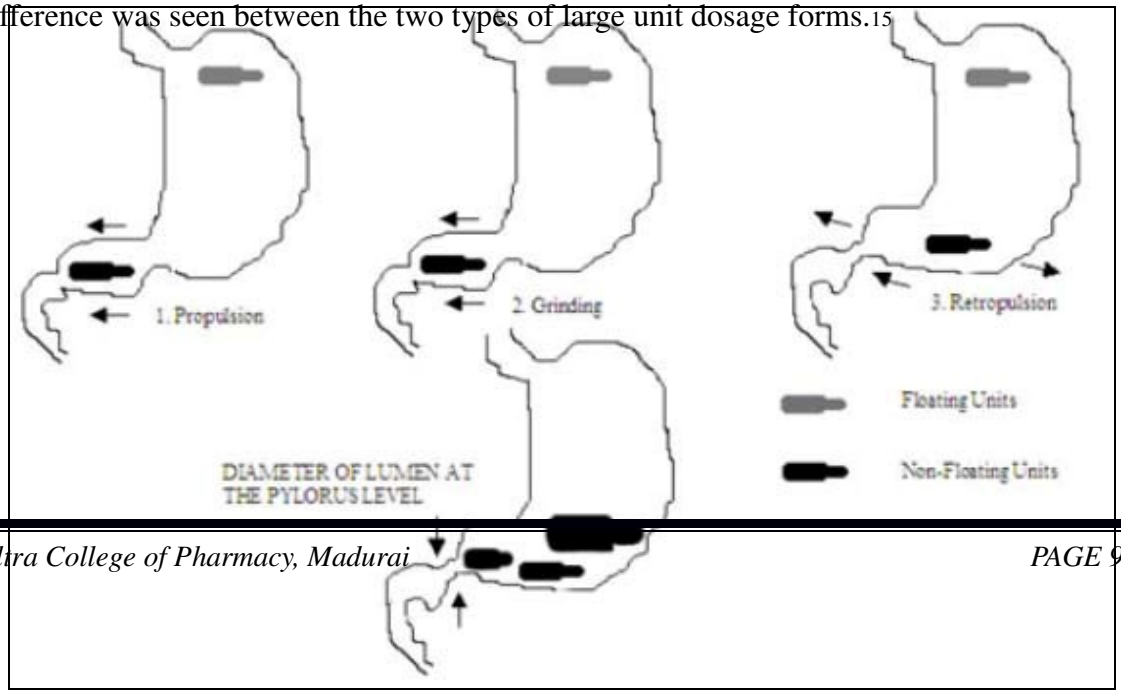


Fig No. 3: Intragastric residence positions of floating and non floating units.

Gastro Retentive Drug Delivery System

Transit of formulation through GIT will determine how long a compound will be in contact with its preferred absorptive site. Absorption windows in proximal gut can limit the bioavailability of orally administered compounds and can be major obstacle in development of controlled release formulations[5]. Two main approaches to increase residence of drug formulations at or above absorption window which have been presently explored:

i) Bioadhesive microspheres that have slow intestinal transit.
ii) Gastro retentive dosage system which is based on multiparticulates or large single unit system.

An elegant and simple way to improve drug absorption is to hold a drug delivery system above the absorption window and for drug to be released at an appropriate rate. Because most absorption windows are thought to be located in proximal small intestine, the obvious strategy will be to hold formulation in stomach (gastro retention)[16]

Pharmaceutical dosage forms with gastro retentive property would enable an extended absorption phase. After oral administration, dosage form would be retained in stomach for several hours and release drug there, in a controlled and prolonged manner, so that drug could be supplied continuously to its absorption sites in upper GIT.

Gastroretention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs of these drugs[17].

Criteria for Selection of Drug Candidate for GRDF

In general, appropriate candidates for CR-GRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

1. Absorption from upper GIT: Drugs have a particular site for maximum absorption e.g. ciprofloxacin, whose maximum absorption is in the stomach only.
2. Drugs having low pKa, which remains unionized in stomach for better absorption.
3. Drugs having reduced solubility at higher pH e.g. captopril and chlordiazepoxide.
4. Local action as it is seen in the treatment of *H.pylori*by amoxicillin and misoprostol as in case of ulcers. The bioavailability of drugs that get degraded in alkaline pH can be increased by formulating gastro retentive dosage forms. E.g. doxifluridine, cefpodoxime proxetil, which degrades in small intestine.
5. To minimize gastric irritation which may be caused by sudden increase of drug concentration in the stomach.e.g. NSAIDs.
6. Improve effectiveness of particular drugs. e.g. Antibiotics in the colon tend to disturb the microflora causing overgrowth of microorganisms like Clostridium difficile causing colitis.
7. Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole[14].

Advantages of Gastroretentive Drug Delivery Systems

1. ***Enhanced bioavailability:***Thebioavailability of riboflavinCR-GRDFis significantly enhanced incomparison to the administration of non-GRDF CR polymeric formulations.
2. ***Enhanced first-pass biotransformation:*** The pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to themetabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.
3. ***Sustained drug delivery/reduced frequency of dosing:*** For drugs with relatively short biological halflife,sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.
4. ***Targeted therapy for local ailments in the upper GIT.***
5. ***Reduced fluctuations of drug concentration.***
6. ***Improved selectivity in receptor activation.***
7. ***Reduced counter-activity of the body:*** Inmanycases,thepharmacological response

which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

8. ***Extended time over critical (effective) concentration:*** For certain drugs that have non-concentration dependent pharmacodynamics, such as betalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.
9. ***Minimized adverse activity at the colon:*** This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.
10. ***Site specific drug delivery:*** The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug.reduces side effects that are caused by the drug in the blood circulation[18].

Disadvantages of gastroretentetive system

There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions and slow release of such drugs in the stomach is unwanted. Thus drugs that may irritate the stomach lining or are unstable in acidic environment should not be formulated as gastroretentive system. Furthermore, other drug such as Isosorbidedinitrate, that are absorbed equally well throughout the GI tract will not benefit by incorporation into a gastric retention system[19].

Also GRDF's have some limitations such as:

1. Requirement of high level of fluids in stomach for the delivery system to float and work efficiently. Drugs, which undergo significant first pass metabolism, may not be desirable candidate for FDDS since the slow GE may lead to systemic bioavailability.
2. Requires the presence of food to delay gastric emptying.
3. Drugs having solubility or stability problems in the highly acidic gastric environment or which are irritant to gastric mucosa cannot be formulated as GRDDS.
4. Gastric emptying of floating dosage forms in supine subjects may occur at random and becomes highly dependent on the diametric size. Therefore, patients cannot be dosed these formulations just before going to bed.
5. On the other hand, violent gas generation, disintegration of dosage forms, burst

release, dose dumping and alkaline microenvironment are the limitations of floating alginate beads.

6. In case of bioadhesive systems, the acidic environment, thick mucous as well as high turnover rate of mucous prevents bond formation at the mucous-polymer interface.
7. For swellable systems, the dosage forms must maintain size larger than the aperture of the resting pylorus for required time period[20].

Approaches to Gastric Retention

A number of approaches have been used to increase gastric retention time (GRT) of a dosage form in stomach by employing a variety of concepts. These include:

(a) Low density form of the DF that causes buoyancy in gastric fluid. (b) High density DF that is retained in the bottom of the stomach.

(c) Bio / Mucoadhesive drug delivery system. (d) Swelling and expanding system.

(e) Incorporation of passage delaying food agents. (f) Ion exchange resin.

(g) Osmotic regulated systems. (h) Raft systems.[3]

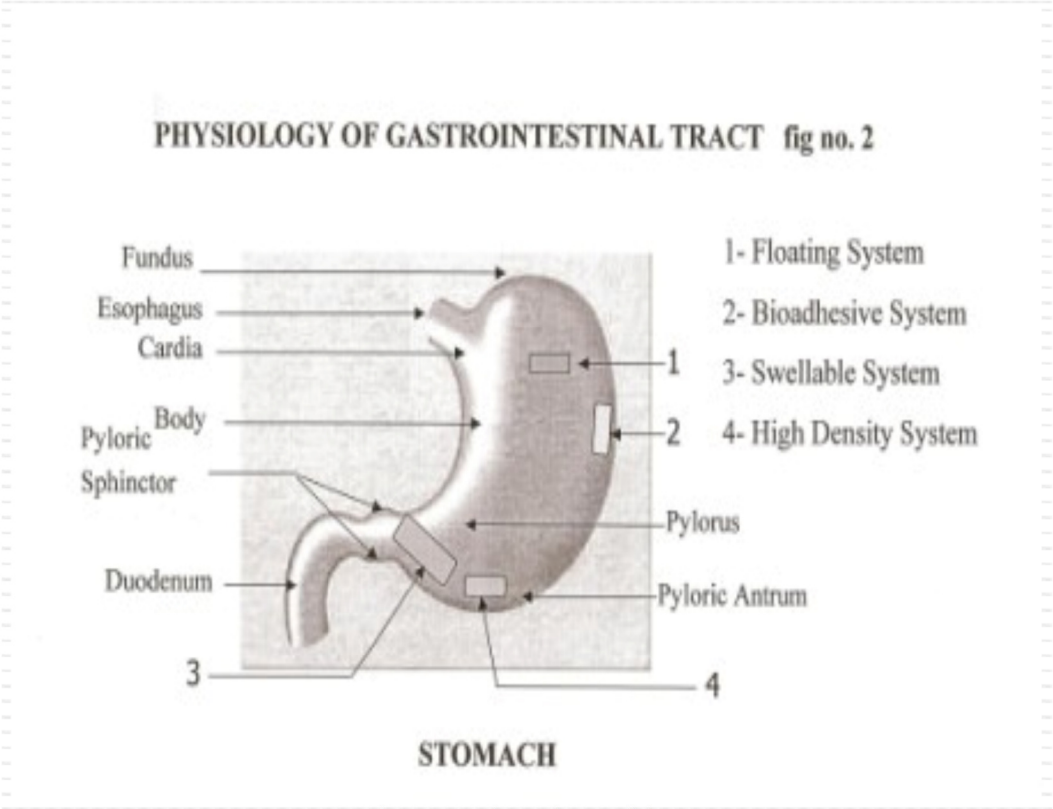


Fig.No.4: Gastric retention sites of different GIRD

a) Floating systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into non-effervescent and effervescent systems.

b) High density systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an uprightposture. These systems have a density of about 3 g/cm3 and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm3 acts as a threshold value after which system can be retained in the lower parts of thestomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.

c) Bio/Muco-adhesive systems

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumento enhance drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach offering possibility of creating an intimate and prolonged contact at site of administration resulting in enhanced absorption and and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc.

Binding of polymers to mucin/epithelial surface can be divided into three broad categories

- Hydration-medicated adhesion.
- Bonding-medicated adhesion.
- Receptor-medicated adhesion.

d) Swelling and expanding system

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systemsmay be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter.They reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach.

e) Incorporation of passage delaying food agents

Food excipients like fatty acids e.g. salt of myristic acid change and modify the pattern of stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C_{10}- C_{14}.

f) Ion exchange resin

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of CO_2. upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate takes place. As a result of this reaction CO_2 was released and trapped in the membrane thereby carrying beads toward the top of gastric content and producing a floating layer of resin beads in contrast the uncoated beads, which will sink quickly[21].

g) Osmotic regulated systems

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intra gastric osmotically controlled drug deliverydevice. The inflatable support inside forms a deformable hallow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two compartment- drug reservoir and osmotically active compartment.

h) Raft forming system

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids. Jorgen *et al* described an antacid raft forming floating system. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus[22].

Floating Drug Delivery Systems (FDDS)

From the formulation and technological point of view, the floating drug delivery systems are considerably easy and logical approach in the development of gastro retentive dosage forms (GRDFs).

Approaches to Design Floating Drug Delivery System

The following approaches have been used for the design of floating dosage forms of single and multiple-unit systems[3].

Classification of FDDS

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS, which are:

A) Effervescent system

Effervescent system include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. Citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it to float on the gastric fluid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. Effervescent systems have been further classified into two types.

I) Gas generating system

a) Intra gastric single layer floating tablets

These systems are formulated by intimately mixing CO_2 generating agents and the drug along with polymers and compressed as a matrix tablet. These have bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after complete release the residual system is expelled from stomach. This leads to an increase in GRT and a better control over fluctuations in plasma drug concentration.

Talwar*et al* prepared a once-daily formulation for oral administration of

ciprofloxacin. The formulation was composed of 69.9% ciprofloxacin base, 0.34%sodium alginate, 1.03% xanthum gum, 13.7% sodium bicarbonate, and 12.1% cross-linked poly vinyl pyrrolidine. The cross linked PVP initially and the gel forming polymers later formed a hydrated gel matrix that entrapped the gas, causing the tablet to float and be retained in the stomach The hydrated gel matrix created a diffusion path for the drug, resulting in sustained release of the drug.

b) Intra gastric bilayered floating tablets

It contains the gas generating mechanism in one hydrocolloid containing layer and drug in other layer formulated for SR effect.

Ozdemir*et al* prepared floating bilayer tablets with controlled release for furosemide. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β cyclodextrin mixed in a 1:1 ratio. One layer contained the polymers HPMC 4000, HPMC 100, and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid.

c) Multiple Unit type floating pills

Ichikawa *et al* developed a new multiple type of floating dosage system having a pill in the core, composed of effervescent layers and swellable membrane layers coated on sustained release pills (shown in figure 5). The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO_2 was generated by the neutralization reaction between the2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml.

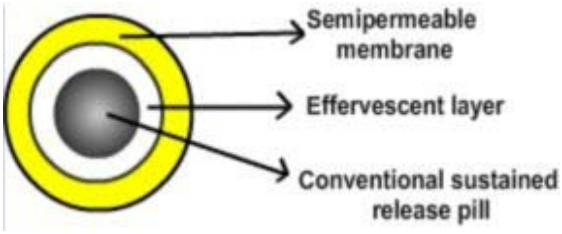


Fig No. 5: Multiple unit type floating pill with different layers.

II) Volatile Liquid / Vacuum Containing System

a) Inflatable gastrointestinal delivery systems

In these systems an inflatable chamber is incorporated, which contains liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the chamber to inflate in the stomach.These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug is continuously released from the reservoir into the gastric fluid.This system shown in figure 6.

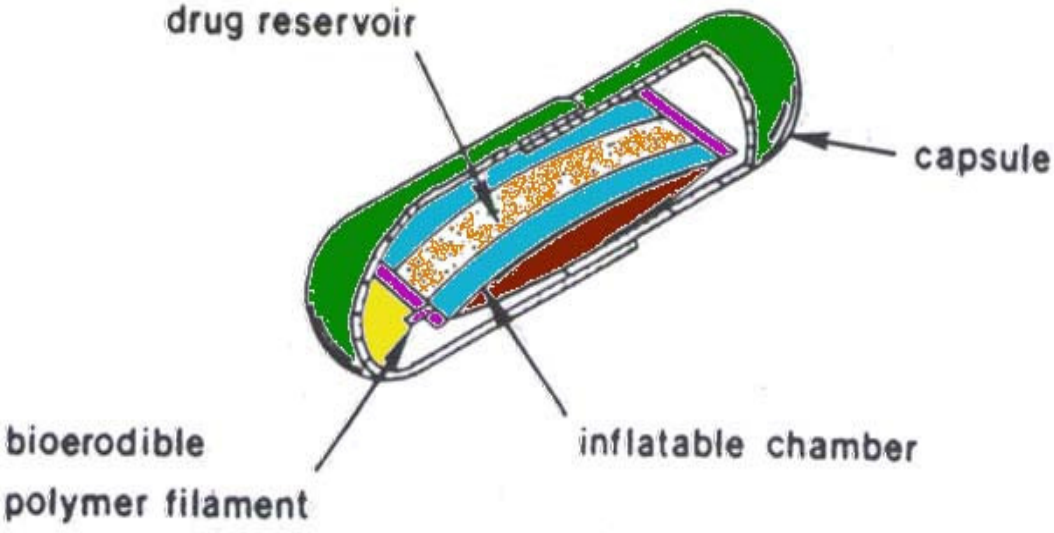


Fig No. 6: Inflatable gastrointestinal delivery systems

b) Intragastricosmotically controlled drug delivery system

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastricosmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled delivery device consists of two compartments; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid that come out from delivery orifice. The osmoticallyactive compartment contains an osmotically active salt and is enclosed within semipermeable housing. In the stomach, water in the GI fluidis continuouslyabsorbedthrough the semipermeable membrane into osmotically active compartment to dissolve the osmotic salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug release of drug solution formulation through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery systemis then emptied from the stomach. This system is shown in figure 7.

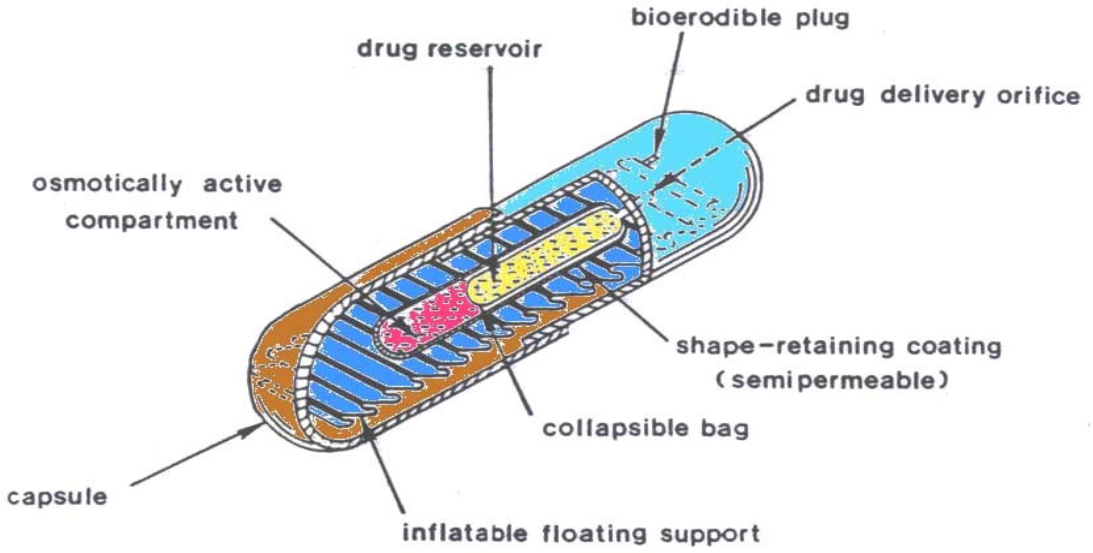


Fig No. 7: Intragastricosmotically controlled drug delivery system

B. Non effervescent systems

The Non effervescent FDDS is based on swelling mechanism of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol[17].

The various type of this systemsare as follows

1. Colloidal gel barrier or Hydrodynamically balanced system (HBS)

It was first designed by Sheth and Tossounian in 1975. These systems are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at outer surface. The air trapped by swollen polymer maintains density less than unity and confors buoyancy. The drug is released progressively fromswollen matrix. E.g. gel forming highly swellable cellulose type hydrocolloids: HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymers such as polycarbophil, polyacrylates and polystyrene.

2. Single layer floating tablets

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid which swell in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

3. Bilayered floating tablets

A bilayered tablet contain two layer- one immediate release layer which release initial dose from system and another sustained release layer which absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface. Since the bulk density of system is less than unity, it remains buoyant in stomach.

4. Microporous compartment system

Fluid- filled floating chamber which includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. TheFluid present could be air, under partial vacuum or any other suitable gas, liquid, or Solid having an appropriate specific gravity and an inert behaviour.

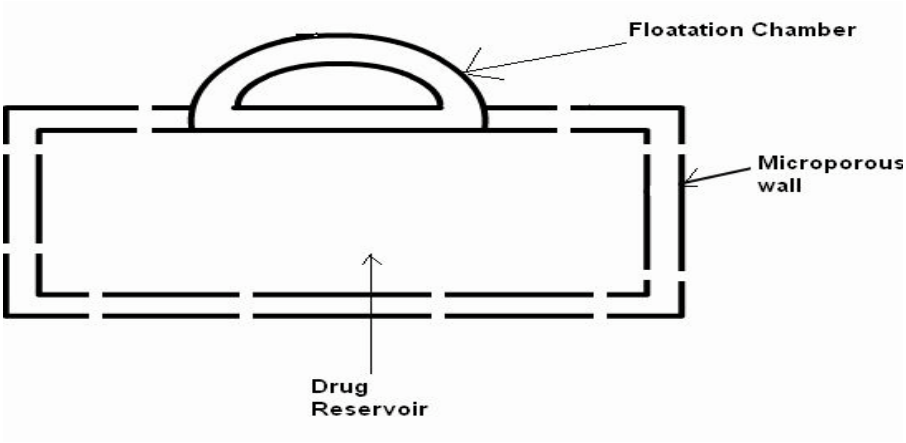


Fig No. 8: Gas filled floatation chamber.

5. Alginate beads

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. These floating beads provide prolonged residence time of more than 5.5 hour.

6. Hollow microspheres

Hollow microspheres (microballons) loaded with drug in their outer polymer shell were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and a enteric acrylic polymer is poured into an agitated aqueous solution of PVA that was thermally controlled at 40ºC. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microspheres of polymer with drug. The microballonsfloated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *In vitro*[18].

Advantages of Hollow Microspheres

1. Improves patient compliance by decreasing dosing frequency.
2. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
3. Gastric retention time is increased because of buoyancy.

4. Enhanced absorption of drugs which solubilise only in stomach
5. Drug releases in controlled manner for prolonged period.
6. Site-specific drug delivery to stomach can be achieved.
7. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
8. Avoidance of gastric irritation, because of sustained release effect.
9. Better therapeutic effect of short half-life drugs can be achieved.

Mechanism of Floating Microspheres

When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy[21, 22]. Hollow microspheres of acrylic resins, eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatableshells; polycarbonate floating balloons and gelucire floating granules are the recent developments[21].

List Of Polymers Used In Hollow Microspheres

Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, Carbopol, Agar, Polyethylene oxide, Polycarbonates, Acrylic resins and Polyethylene oxide.

Table No. 2: Various Types of Floating Drug Delivery Systems studied

Name of formulation	Name of drug
Tablets	Ampicillin, Atenolol, Amoxycillin, Acetyl salicylic acid, Acetaminophen, Chlorpheniramine maleate, Ciprofloxacin, captopril, Cinnarazine, Dilitazem, Fluoruracil, Isosorbide di nitrate, Riboflavin, Prednisolone, Theophilline.
Capsules	Nicardepine, Diazepam, Misoprostol, Propranolol, Verapamil.
Microspheres/Floating beads	Aspirin, Verapamil, Ibuprofen, Ketoprofen, Amoxicillin, Riboflavin, Meloxicam, Nicardepine etc.
Granules	Indomethacin,Diclofenac, Prednisolone[23].

Table No. 3: Marketed products of GRDFs

SR.NO.	BRAND NAME	DRUG (DOSE)	COMPANY, COUNTRY	REMARKS
1.	Madopar®	Levodopa (100 mg) Benserazide	Roche Products,USA	Floating CR capsule
2.	Valrelease®	Diazepam (15mg)	Hoffmann-LaRoche,USA	Floating Capsule
3.	Liquid Gaviscon®	Al hydroxide (95 mg), Mg carbonate (358 mg)	GlaxoSmithKline, India	Effervescent floating liquid alginate
4.	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid alginate
5.	Conviron	Ferrous sulphate	Ranbaxy, India	forming FDDS
6.	Cifran OD®	Ciprofloxacin (1mg)	Ranbaxy, India	Gas-generating
7.	Cytotec®	Misoprostol (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating
8.	Oflin OD®	Ofloxacin (400 mg)	Ranbaxy, India	Gas-generating

LITERATURE REVIEW

A.H. El-Kamel et al., (2000) prepared the Ketoprofen floating oral delivery system by the emulsion solvent diffusion technique. Four different ratios of Eudragit S100 (ES) with Eudragit RL (ERL) were used to form the floating microparticles. The drug retained in the floating microparticles decreased with increase in ERL content. All floating microparticle formulations showed good flow properties and packability. Scanning electron microscopy and particle size analysis revealed differences between the formulations as to their appearance and size distribution. X-ray and DSC examination showed the amorphous nature of the drug[41].

K**umaresh S et al**, (2001) investigated the release characteristic of hollow microspheres of cellulose acetate loaded with four cardiovascular drugs (nifedipine [NFD], nicardapine hydrochloride [NCD], verapamil hydrochloride [VRP], and dipyridamole [DIP]) prepared by a novel solvent diffusion evaporation method. They found that yield of microspheres was 80% and microspheres tended to float over the gastric media for more than 12 hr. The release of the drug was controlled for more than 8 hr. Finally they concluded that drugs like nifidipine and nicardipine hydrichloride can be delivered for effective management of hypertension[35].

Sato Y et al, (2003) Prepared and evaluated riboflavin containing microballoons for floating controlled drug delivery system in healthy humans. They observed strong correlation between the buoyancy and excretion half-life ($t_{1/2}$) and riboflavin release from the microballoons and total urinary excretion. Finally they concluded that the intragastric floating properties of microballoons are likely to be beneficial as far as a sustained pharmacological action is concerned[26].

Yasunori sato et al, (2004) Reported on the floating and drug releasing behaviors of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method. Microballoons were prepared by utilizing enteric acrylic polymers codissolved with drug in a mixture of dichloromethane and ethanol. The release properties of five different drugs exhibiting distinct water solubilities (aspirin, salicylic acid, ethoxybenzamide, indomethacin and riboflavin) entrapped within microballoons were investigated. They concluded that

Buoyancy of the microballoons decreased with increasing drug release rate. In the case of aspirin, salicylic acid and ethoxybenzamide, the drug release profiles of microballoons proved a linear relationships by Higuchi plotting. In addition, by incorporating a polymer such as hydroxypropylmethylcellulose within the shell of microballoons, the release rate of riboflavin from the microballoons could be controlled while maintaining high buoyancy[32].

Jain SK et al, (2005) prepared porous carrier based floating granular delivery system of Repaglinide using calcium silicate as porous carrier, HPMC K4M, ethyl cellulose and carbopol 940 as matrix forming polymers and evaluated for its gastro retentive and controlled release properties, particle morphology, micromeritic properties, invitro floating behaviour, drug content (%), invitro drug release, comparison with marketed capsule and *invivo* study in albino rat52.

Streubel A et al, (2006) developed and evaluated a novel preparation method for floating microparticles consisting of polypropylene foam powder, of chlorpheniramine maleate, diltiazem HCl and theophylline or verapamil HCl) as model drugs with polymers like eudragit RS or polymethacrylate. They concluded that new preparation methods have short processing time, no exposure of ingredient to high temperature and avoid use of toxic organic solvent, no drug loss and encapsulation efficiency close to 100%28.

Patel A et.al. (2006) prepared and optimized the floating microspheres of metformin hydrochloride using ethyl cellulose and concluded that the developed floating microspheres of metformin hydrochloride may be used in clinic for prolonged drug release in stomach for at least 8 hrs, thereby improving the bioavailability and patient compliance[34].

Shraddha S. Badve et al., (2006) developed porous calcium pectinate beads for floating-pulsatile drug delivery. The floating beads obtained were porous (34% porosity), hollow with bulk density <1 and had t50% of 14-24 h. *In-vivo* studies by gamma scintigraphy determined

on rabbits showed gastroretention of beads up to 5 h41.

Ramesh.R.Putheti1 et al, (2009) reviewed Pharmaceutical Formulation and development of Floating and Swellable sustained drug delivery systems various parameters affecting the behavior of floating and swelling multiparticulate in oral dosage form summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating and swellable systems, and applications of these systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form. From the formulation and technological point of view, the floating and swellable drug delivery systems are considerably easy and logical approach. An attempt has been made in this review article to introduce scientists to the current technological developments in floating and swellable drug delivery system[37].

Rajinikanth PS, (2009) et al., developed a stomach-specific drug delivery system for controlled release of clarithromycin for eradication of *Helicobacter pylori* (*H. pylori*). Floating-bioadhesive microspheres of clarithromycin (FBMC) were prepared by emulsification-solvent evaporation method using ethylcellulose as matrix polymer and Carbopol 934P as mucoadhesive polymer. The prepared microspheres were subjected to evaluation for particle size, incorporation efficiency, *in vitro* buoyancy, *in vitro* mucoadhesion and *in vitro* drug release characteristics. The prepared microspheres showed a strong mucoadhesive property with good buoyancy. The formulation variables like polymer concentration and drug concentration influenced the *in vitro* drug release significantly in simulated gastric fluid (pH 2.0). The *in vivo H. pylori* clearance efficiency of prepared FBMC in reference to clarithromycin suspension following repeated oral administration to *H. pylori* infected Mongolian gerbils was examined by polymerase chain reaction technique and by a microbial culture method. The FBMC showed a significant anti-*H. pylori* effect in the *in vivo* gerbil model. It was also noted that the required amount of clarithromycin for eradication of *H. pylori* was significantly less in FBMC than from corresponding clarithromycin suspension. The result further substantiated that FBMC improved the gastric stability of clarithromycin (due to entrapment within the microsphere) and eradicated *H. pylori* from the gastrointestinal tract more effectively than clarithromycin suspension because of the prolonged gastrointestinal residence time of the formulation[33].

Vishal G Karkhile et al., (2009) prepared the floating tablets of Furosemide by direct compression technique. The tablets were evaluated for *in-vitro* buoyancy and dissolution studies. Tablets were evaluated for physical characteristics viz. Hardness, floating capacity, thickness, swelling index, and weight variation. Further, tablets were evaluated for *in-vitro* release characteristic for 8 hours. The data of *in-vitro* dissolution study shows that the zero order plots were found to be fairly linear as indicated by their high regression value (R2 = 0.9772 to 0.9911)40.

Shah S.H et al, (2011) reviewed on the stomach specific floating drug delivery system: a review It is known that differences in gastric physiology, such as, gastric pH, and motility exhibit both intra-as well as inter-subject variability demonstrating significant impact on gastric retention time and drug delivery behaviour. This triggered the attention towards formulation of stomach specific (gastro retentive) dosage forms. This dosage forms will be very much useful to deliver 'narrow absorption window' drugs. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recent developments of Stomach Specific FDDS are discussed[36].

N.V.Satheesh Madhav, (2011) reviewed on various aspects of the microparticulate drug dlivery system including method of formation, evaluation and characterization43.

Yogesh Garg et al, (2011) prepared the purified microparticles of Pravastatin sodium use for intestinal delivery. Microparticles formed were discrete, free flowing, and exhibited good mucoadhesive properties. DSC and DRS showed stable character of drug in microparticles and absence of drug polymer interaction. The drug to polymer ratio and surfactant concentration had significant effect on mean particle size, drug release, and entrapment

efficiency. *In-vitro* permeation studies on goat intestinal mucosa demonstrated a flux rate that was 169 times higher than the flux of pure drug42.

Ashish Gupta et al, (2012) prepared the Repaglinide microspheres by Quasi emulsion solvent diffusion technique. The microspheres were formulated by using various concentration of HPMCP, Ethyl cellulose and Eudragit RSPO as a retarding agent to controll the release rate. The prepared microspheres were evaluated for Flow behaviour, Compatibility study, Drug entrapment efficiency, *In-vitro* dissolution, Scanning electron microscopy and particle size analysis. *In-vitro* release studies indicated that, as the concentration of retarding agent increases release from the formulation become more sustained38.

SCOPE OF THE WORK

To develop oral drug delivery systems, it is necessary to optimize both the residence time of system within the gastrointestinal tract and release of drug from the system. Gastric emptying of dosage form is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage form. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drug and improves bioavailability, reduces drug waste and improves solubility, of drug that are less soluble in a high pH environment.

Clarithromycin is an advanced generation macrolide antibiotic used in treatment of H. Pylori. Besides multi-antibiotic therapy, one of the strategies that can completely eradicate H.pylori from the stomach and improve the efficacy is to deliver the antibiotic locally in the stomach by increasing residence time of antibiotics at infected site. Another way is to improve the stability of an antibiotic in gastric environment. The antibiotics with better stability and longer residence time will allow more of the antibiotic to penetrate through the gastric mucus layer to act effectively on H.pylori. Then clarithromycin penetrates bacteria cell wall and reversibly binds to domain V of the 23S ribosomal RNA of the 50S subunit of the bacterial ribosome, blocking translocation of aminoacyl transfer-RNA and polypeptide[25]

The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion, flotation, sedimentation, expansion, modified shape system or by the simultaneous administration of pharmacological agents that delay gastric emptying. Floating microparticls are gastro retentive drug delivery systems based on non- effervescent approach. These microparticles are characteristically free flowing powders and remain buoyant over gastric contents for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Drugs having short half life are eliminated quickly from the blood circulation and hence require frequent dosing. To avoid this, release of drug will be made slowly in the gastrointestinal tract and maintain effective drug concentration in the serum for longer period of time[30].

A controlled release system designed to increase its residence time of clarithromycin in the stomach can be achieved through the preparation of floating delivery systems either tablets or microspheres.

Floating multiparticulate dosage form have been prepared by solvent diffusion and solvent evaporation method to create an hollow inert core [26, 27]. Porous calcium pectinate beads with bulk density less than 1 were prepared by Badve SS. Alternatevely floating microparticles based on low density foam powder were prepared with polypropylene foam powder, matrix forming polymer and the drug (Verapamil HCL)[28]. Instead of foam powder highly porous carrier material like calcium silicate was used along with Eudragit S to deliver Repaglinide over an extend period of time.

In the present study, colloidal silicon dioxide (Aerosil) was used as the porous material. Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying[29]. One study reveals the use of calcium silicate as porous carrier. The present study was aimed at using colloidal silicon dioxide as porous carrier for preparing floating microparticles of Clarithromycin whose physiochemical properties and short half life make it suitable candidate for floating drug delivery system[31].

OBJECTIVE OF THE WORK

The main objectives of the present work are

- To prepare the floating microparticles of the Clarithromycin with the use of polymer-ethyl cellulose, aerosil and different solvents (dichloromethane & ethanol).
- To evaluate the formulated floating microparticles for various characteristics and properties and to arrive at the optimized formulation based on floating time and *in vitro* drug release.

PLAN OF WORK

1. Literature review to select method of preparation of floating microparticles of Clarithromycin.
2. Preformulation studies
   - Determination of Solubility of Clarithromycin.
   - Preparation of calibration curve of Clarithromycin.
   - FT-IR Spectroscopy.
3. Formulation development of floating microparticles of Clarithromycin.
4. Evaluation of prepared Clarithromycin microparticles.
   - Micromeritic Properties of microparticles (particle size, bulk density, tapped density, compressibility index, hausners ratio, angle of repose).
   - Percent yield of microparticle.
   - Drug entrapment efficiency.
   - Morphology by SEM.
   - Crushing strength..
   - *In-vitro* drug release studies.

MATERIALS AND METHODS

List of Materials

TABLE:4 List of materials

S.No	Chemicals & reagents	Supplier
1	Clarithromycin	RA CHEM pharma
2	Ethyl cellulose	S.d Fine- chem. Ltd
3	Colloidal silicon dioxide	SRL
4	Dichloromethane	SRL
5	Ethanol	Trade Co.Ltd made in china

List of Instrument/ Equipments

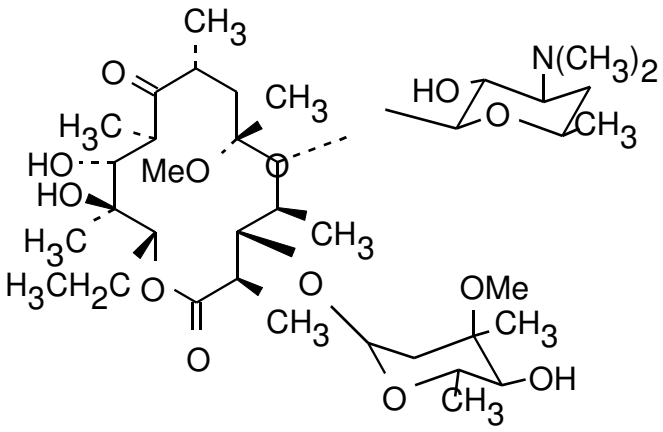
TABLE:5 List of Instruments and uses

S.No	**Instrument/ Equipment**	**Source**
1	Electronic balance	Shimadzu corporation, Japan
2	Mechanical stirrer	Remi motors, Mumbai
3	FT-IR Spectroscopy	Perkin Elmer
4	Sieves	Jayant scientific Ltd- mumbai
5	Scanning electronic microscope	Tescan
6	Phase contrast microscope	Bino cxi micron optic
7	T.A.X.T plus Texture Analyser	Stable micro system, UK
8	UV-Visible spectro photometer	Systronics
9	Dissolution test apparatus	Disso 2000 Lab india
10	Vacuum oven	Shivani scientific industries p (Ltd) Bombay

DRUG PROFILE

CLARITHROMYCIN

Structure:



Clarithromycin

Chemical Name: 6-O-methylerythromycin

Empirical formula: $C_{38}H_{69}NO_{13}$

Molecular Weight: 747.95

Melting Point: 220^0C

Description: White or colourless, odourless crystals.

Category: Antibacterial

Storage: Store in a cool, dry place.

Solubility:

It is soluble in chloroform, acetone and dilute acids. Slightly soluble in methanol, ethanol and acetonitrile, and practically insoluble in water[54].

Pharmacodynamic Property:

Clarithromycin is a semi-synthetic broad spectrum macrolide antimicrobial agent structurally related to Erythromycin. It is acid stable and rapidly absorbed after oral administration.

Clarithromycin is bacteriostatic or bacteriocidal depending on the organism and antimicrobial agent concentration. It exerts its antibacterial action by binding to the 50S ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram- positive and gram-negative organisms such as *S.aureus, S.pneumoniae, H.influenza, Moraxella catarrhalis*, and other microorganisms like *Mycobacterium avium complex* (MAC) and *Helicobacter pylori.*

Pharmacokinetic Property:

Absorption: - Clarithromycin is absorbed rapidly from the gastrointestinal tract after oral administration. The microbiologically active metabolite 14-hydroxy Clarithromycin is formed by first pass metabolism. Peak concentration occurs approximately 2 hrs after drug administration. Steady state peak concentration in plasma are 2 to 3 mg/ml after 2 hours from a regimen of 500 mg every 12 hours or 2 to 4 hours after two 500 mg extended release tablets given orally.

Distribution: - Clarithromycin and its active metabolite 14-hydroxy Clarithromycin distribute widely throughout the body and achieve high intracellular concentrations. Tissue concentrations generally exceed serum concentrations. Concentrations in middle ear fluid are 50% higher than simultaneous serum concentrations for both Clarithromycin and the active metabolite. Protein binding of Clarithromycin ranges from 40-70%.

Elimination: - Clarithromycin is eliminated by renal and non-renal mechanisms. It is metabolized in the liver to active 14-hydroxy metabolite. The elimination half- lives of Clarithromycin and 14-hydroxyclarithromycin are approximately 3 to 7 hours and 5 to 9 hours. The amount of Clarithromycin excreted unchanged in the urine ranges from 20% to 40% depending on the dose administered and formulation.

Therapeutic Uses:

- Used in combination for the treatment of *Helicobacter pylori* infection and duodenal ulcer disease.
- For treatment of upper and lower respiratory tract infections.
- For prevention of disseminated Mycobacterium avium complex (MAC) infections in patients with advanced human immunodeficiency virus (HIV) infections.
- Uncomplicated skin and skin structure infections like Folliculitis, Cellulitis, Erysipelas.

Adverse Effects:

The majority of the adverse effects reported were of mild and transient nature like Diarrhoea, nausea, abnormal taste, dyspepsia, headache, etc.

Dosage and Administration:

Clarithromycin is used orally in a dose of 250 to 500mg twice daily.

Marketed Preparations:

CELEX OD (Abott) 500 mg

Clarithro ER (Alembic) 500 mg

URCLAR OD (Novartis) 500 mg

MACLAR (Gracewell) 500 mg[55]

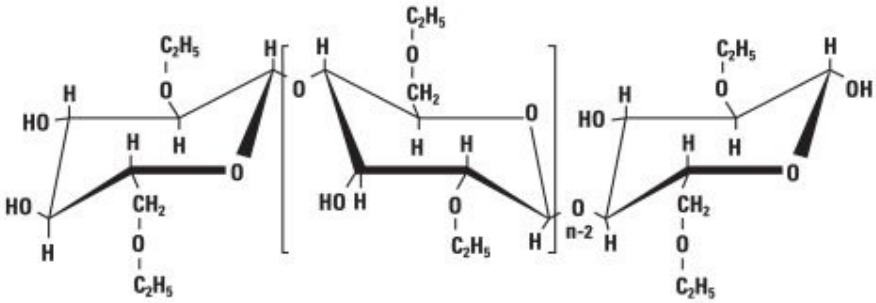
EXCIPIENT PROFILE

1. Ethyl cellulose (EC)

Synonyms: Aquacoat E-462, Ethocel, Surelease.

Functional category: Coating agent, tablet binder and viscosity increasing agent.

Structural formula:



Description: Ethyl cellulose is a tasteless, free flowing white light coloured powder.

Solubility:

1. Ethylcellulose is practically insoluble in glycerine, propylene glycol and water.
2. EC that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol, ethyl acetate, methanol and toluene.

Melting point: Glass transition temperature – 129-133ºC.

Stability and Storage Conditions: Ethyl cellulose is stable, slightly hygroscopic materials. It is subjected to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. It should not be stored at temperature exceeding 32ºC (90ºF).

Safety: Ethyl cellulose is widely used in oral and topical pharmaceutical formulations. It is not metabolized following oral consumption and is therefore a non-calorific substance. Ethyl cellulose is generally regarded as non-toxic, non- allergic and non-irritating material.

Handling Precautions: It is important to prevent fine dust clouds of ethyl cellulose from reaching potentially explosive levels in air. Ethyl cellulose is combustible. EC powder may be an irritant to the eyes and eye protection should be worn.

2. Colloidal Silicon Dioxide

Synonyms:

Aerosil, Cab-O-Sil, colloidal silica, light anhydrous silicic acid, silicic anhydride, Silicon dioxide fumed.

Description:

Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15nm.It is a light, loose, bluish-white-colored, odorless, tasteless, non-gritty amorphous powder**.**

Chemical Name: Silica

Empirical Formula: SiO_2

Molecular Weight: 60.08

Functional Category: Adsorbent, anti caking agent, glidant, tablet Disintegrant, viscosity-increasing agent.

Application in Pharmaceutical Formulation:

- Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products.
- Colloidal silicon dioxide is also used to stabilize emulsions and as a thyrotrophic thickening and suspending agent in gels and semisolid preparations.

- Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent, dispersing agent for liquids in powders.

Stability and Storage Condition:

- Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying.
- Colloidal silicon dioxide powder should be stored in well-closed container.

Incompatibilities:

Incompatible with diethylstilboestrol preparations.

Safety: Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially non-toxic and non-irritant excipient[56].

EXPERIMENTAL SECTION

Preformulation studies

Preformulation testing is the first step in the rational development of dosage forms of the drug. It can be defined as investigation of physical and chemical properties of drug substance, alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced.

A thorough understanding of physicochemical properties may ultimately provide a rational for formulation design or support the need for molecular modification or merely confirm that there are no significant barriers to the compounds development. The goals of the program therefore are

- To establish the necessary physicochemical characteristic of a new drug substance.
- To establish its compatibility with different excipients.

Solubility analysis

Preformulation solubility analysis was done to select a suitable solvent system to dissolve the drug as well as various excipients used for formulation and also to test drugs solubility in the dissolution medium, which is to be used.

Preparation of calibration curve for Clarithromycin

Preparation of Potassium dihydrogen ortho phosphate solution

0.476 g of potassium dihydrogen ortho phosphate was dissolved in water and made up to 100 ml with water and added one drop of orthophosphoric acid to make pH 4.4.

Procedure for construction of calibration curve of Clarithromycin

Clarithromycin, 25 mg was dissolved in 50 ml of Potassium dihydrogen ortho phosphate solution pH 4.4 (500µg/ml). From it, 5 ml was withdrawn and volume was made up to 50 ml with Potassium dihydrogen ortho phosphate buffer pH 4.4 (stock solution 50µg/ml). A series of dilutions were made from the above stock solution to get the solutions of concentration ranging from 20-100 µg/ml. From this solution 1 ml solution was taken and add 2 ml Folin reagent (1 ml diluted with 2 ml water) & add 2 ml 20 % sodium caronate and add potassium dihydrogen ortho phosphate buffer to make 10 ml, absorbance of solutions were measured visible spectrophotometrically at 760 nm.

Compatibility studies of Clarithromycin and polymers

FTIR spectra help to confirm the identity of the drug and to detect to the interaction of the drug with the carriers.

Infrared Spectroscopy

The IR absorption spectra of Clarithromycin, Ethyl cellulose, Colloidal silicon dioxide alone and in combination were determined by Fourier Transform Infrared spectrophotometer using KBr dispersion method. The obtained spectra were analysed for functional group of the drug and polymer.

Formulation of Floating microspheres of Clarithromycin

All the formulations were prepared according to the formula given in Table 6. The microparticles were prepared by using ethyl cellulose as matrix material and colloidal silicon dioxide (Aerosil) was used as porous material. In the first six formulations Clarithromycin and Ethyl cellulose were dissolved in dichloromethane (F1-F6) and next six formulations (F7-F12) Clarithromycin and Ethyl cellulose were dissolved in ethanol, then aerosol (colloidal silicon dioxide) was suspended uniformly in drug polymer solution. The solution was stirred with a propeller-type agitator at room temperature for 1 hr at 150 rpm. The formed floating microparticles were dried at room temperature in desiccators.

FORMULATION DESIGN

Table No.6: Composition of Clarithromycin floating microspheres.

Materails	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
DRUG (CLARITHROMYCIN)(mg)	500	500	500	500	500	500	500	500	500	500	500	500
ETHYL CELLULOSE (mg)	–	50	100	200	300	400	–	50	100	200	300	400
AEROSIL (mg)	50	50	50	50	50	50	50	50	50	50	50	50
DICHLOROMETHANE(ml)	10	10	10	10	10	10	–	–	–	–	–	–
ETHANOL (ml)	–	–	–	–	–	–	10	10	10	10	10	10

EVALUATION OF FLOATING MICROPARTICLES

Scanning electron microscopy

Scanning electron microscopic studies were was carried out on formulation F2. Dry microparticles were placed on an electron microscope brass stub a coated with gold in an ion sputter. Then picture of microparticle were taken by random scanning of the stub. The SEM analysis of the microspheres was carried out by using Tescan analytical scanning electron microscope. The microspheres were viewed at an accelerating voltage of 20KV.

Micromeritic properties

The microparticles were characterized by their micromeritic properties such as particle size, bulk density, tapped density, compressibility index, Hausners ratio and angle of repose[44].

a. Weight distribution of microparticles

Size distribution of the microparticles was determined by using standard test sieves. Microparticles retained on the sieves were collected and weighed and the distribution was analysed based on the weight fraction on each sieve[57].

b. Bulk density

In this method floating microparticles are transferred to a measuring cylinder and is tapped manually till a constant volume is obtained. This volume is bulk volume and it includes true volume of the powder and the void space among the microparticles [58]

Bulk density = Mass of microparticle/ Bulk volume

c. Tapped density

In this method floating microparticles were transferred to a measuring cylinder & tapped for 100 times. After tapping volume of microparticles was visually examined. The ratio of mass of microspheres to volume of microspheres after tapping gives tapped density floating microspheres[44, 58].

Tapped density = Mass of microparticles/ Volume of microparticles after tapping

c. Carr's Compressibility index

Carr's Compressibility index was determined by using the formula,

Carr's Compressibility index = $1-V/V_0$

Here V and V_0 are the volumes of the sample after and before the standard tapping, respectively[57].

Table No.7: Relalationship between Carr's compressibility index and flowability

Carr's Compressibility index	Flowability

5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

d. Hausners ratio

Hausners ratio of microparticle was determined by comparing tapped density to bulk density using the equation[58]

Hausners ratio = Tapped density / Bulk density

e. Angle of repose

Angle of repose (θ) of the micro particle, which measures the resistance to particle flow, was determined by a fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed microparticles were allowed to pass through the funnel freely onto the surface. The height and radius of the powder cone was measured and angle of repose was calculated using the following equation[44].

$\theta = \tan^{-1} h/r$

Where,

θ = Angle of repose

h= Height of granules above the flat surface

r= Radius of the circle formed by the granule heap

Table No.8: Relationship between angle of repose and flowability

Angle of Repose	**Flowability**
<20	Excellent

20-30	Good
30-34	Passable
>40	Very poor

Yield of floating microspheres

The prepared floating microparticles were collected and weighed. The measured weight was divided by total amount of all non volatile components which were used for the preparation of microparticles.

% yield = (Actual weight of product/ Total weight of excipient and drug) × 100

In-vitro Buoyancy

Floating microparticles (equivalent to 500 mg) were dispersed in 900 ml of 0.1N hydrochloric acid solution containing tween 80 (0.01w/v %) /tween 20 (0.02w/v %) to simulate gastric fluid at 37^0C. The mixture was stirred with a paddle at 100 rpm and after 12 hr; the layer of buoyant microparticle (W_f) was pipette and separated by filtration. Simultaneously sinking microparticle (W_s) was also separated. Both microparticle types were dried at 40^0C overnight. Each weight was measured and buoyancy was determined by the weight ratio of the floating microparticle to the sum of floating and sinking microparticle.

$$\text{Buoyancy } (\%) = [W_f/(W_f+W_s)]\times 100$$

Where Wf and Ws are the weights of the floating and settled microparticle respectively.

Incorporation efficiency

Floating microparticles were dissolved in a minimum amount of methanol and drug was extracted into 0.1 N hydrochloric acid by evaporating methanol. The solution was filtered through whatman filter paper, diluted suitably and analyzed for drug content visible spectophotometrically at 760 nm using 0.1N hydrochloric acid as blank.

Crushing strength

Sample Preparation:

Strips of adhesive tape correspond to the P/25 probe. The strips of tape (adhesive side upwards) onto a clean surface and gently pour the sample over the tape. After application of the sample, lift the tape and gently shake to ensure an even covering of the surface. Tip the excess sample off.

Test Set-Up:

Before testing, the probe must be calibrated against the machine base and returned to a set distance (It is important to start all tests from the same distance above the machine base for comparison when a button trigger is specified). The prepared tapes are placed under the clean probe, after ensuring the surface under the tape is completely flat and clean of debris, which would produce erroneous results. The compression test is commenced and repeated on other regions of the tape.

In-vitro Drug release

Floating microparticle equivalent to 500 mg of drug was carried out using paddle method at 50 rpm, up to 3 hrs. 2ml of sample were withdrawn at different time intervals and replaced with 0.1N HCl, and make up to 10 ml with buffer. From this solution 1 ml solution was taken and add 2 ml Folin reagent (1 ml diluted with 2 ml water) & add 2 ml 20 % sodium carbonate and add 0.1N HCl to make 10 ml, the amount of drug release was analyzed at 760 nm using Systronics visible spectrophotometer.

RESULTS

In this present study Clarithromycin microparticles were prepared by using by using ethyl cellulose as matrix material and colloidal silicon dioxide (Aerosil) as porous material. The solvents, dichloromethane and ethanol were used for the preparation of microparticles.

PREFORMULATION STUDIES

a) Standard calibration curve of Clarithromycin

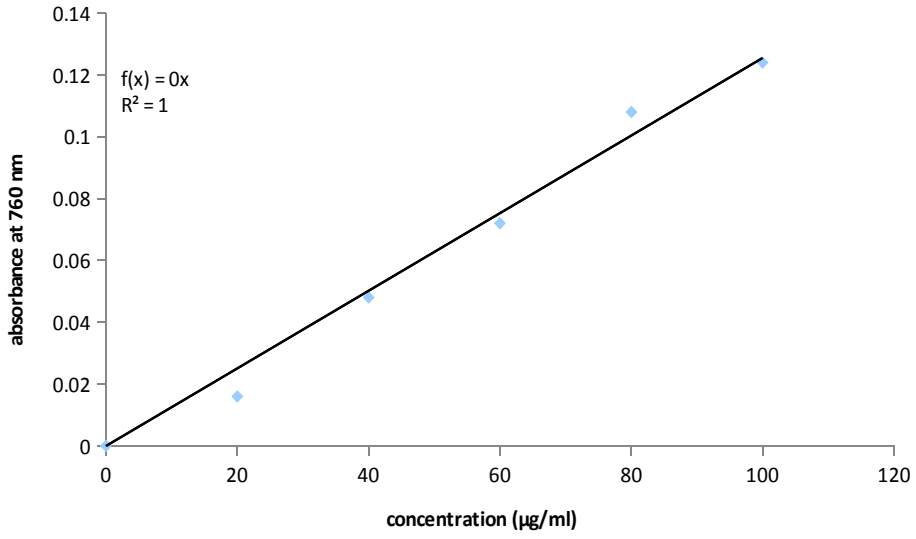
A calibration curve (fig 9) was plotted by taking the different concentration of Clarithromycin i.e. from 20 to 100 µg/ml on X-axis and obtained absorbance at 760nm on Y-axis. The data are given in Table. 9 and the figure is given below

Absorbance values of Clarithromycin in Potassium dihydrogen ortho phosphate buffer Ph 4.4 at 760nm

TABLE:9

S.No	Concentration µg/ml	Absorbance at 760 nm
1	0	0
2	20	0.016
3	40	0.048
4	60	0.072
5	80	0.108
6	100	0.124

Fig : 9 : Standard calibration curve for Clarithromycin



b) Infrared Spectroscopy study

IR spectral studies for the identification of pure Clarithromycin, Ethyl cellulose, Aerosil and mixture of Drug & Aerosil and Drug, Ethyl cellulose & Aerosil shows no interaction between them, which indicate that the drug is compatible with Ethyl cellulose and colloidal silicon dioxide and hence safe and stable formulations can be made.

The IR Spectra are given in fig 10-14; Table.10 shows the wave number for group assigned in the infrared spectra of pure drug Clarithromycin.

Table No: 10

IR spectral data of pure Clarithromycin

S.No	Frequency (cm^{-1})	Group Assigned
1	3470.94	O-H Stretching vibration
2	2976.29	C-H Stretching vibration
3	2940.95	C-H Stretching vibration
4	1732.75	C-O Stretching vibration
5	1692.23	C=O Stretching vibration
6	1051.73	O-H Stretching vibration
7	1010.48	C-O Stretching vibration
8	1251.69	C-N Stretching vibration
9	1282.51	C-N Stretching vibration
10	1109.50	C-O-C stretching vibration
11	839	C-H deformation

Infrared spectra for pure Ethyl cellulose polymer was identified by using Fourier transform infrared spectrometer by using KBr disk method.

The following Table 11 shows the wave number for group assigned in the infrared spectra of pure Ethyl cellulose

Table no: 11

IR spectra data of pure Ethyl cellulose

S.No	Frequency (cm^{-1})	Group Assigned
1	3481.81	O-H Stretching
2	2977.45	C-H Stretching
3	2875.55	C-H Stretching
4	1312.60	C-O Stretching
5	1379.10	O-H deformation
6	881.09	C-H deformation
7	1111.89	C-O-C stretching vibration

Infrared spectra for pure Aerosil was identified by using Fourier transform infrared spectrometer by using KBr disk method.

The following table.12 shows the wave number for group assigned in the infrared spectra of pure Ethyl cellulose

Table no: 12

IR spectra data of pure Aerosil

S.No	Frequency (cm^{-1})	Group Assigned
1	3427.39	O-H Stretching
2	2928.16	C-H Stretching
3	1720.31	C-O Stretching
4	807.47	C-H deforming
5	1102.53	O-H Stretching

FTIR spectra data for mixture contain Clarithromycin & Aerosil were identified the wave number for group assigned in the infrared spectra shown in following table.13

Table No :13

IR spectral data of physical mixture of Clarithromycin & Aerosil

S.No	Frequency (cm^{-1})	Group Assigned
1	3467.06	O-H Stretching
2	2976.74	C-H Stretching

3	1734.23	C-O Stretching
4	1656.02	C=O Stretching
5	1103.50	C-O-C Strtching
6	806.13	C-H deformation
7	1580.95	C=C Stretching
8	1459.51	C-H deformation

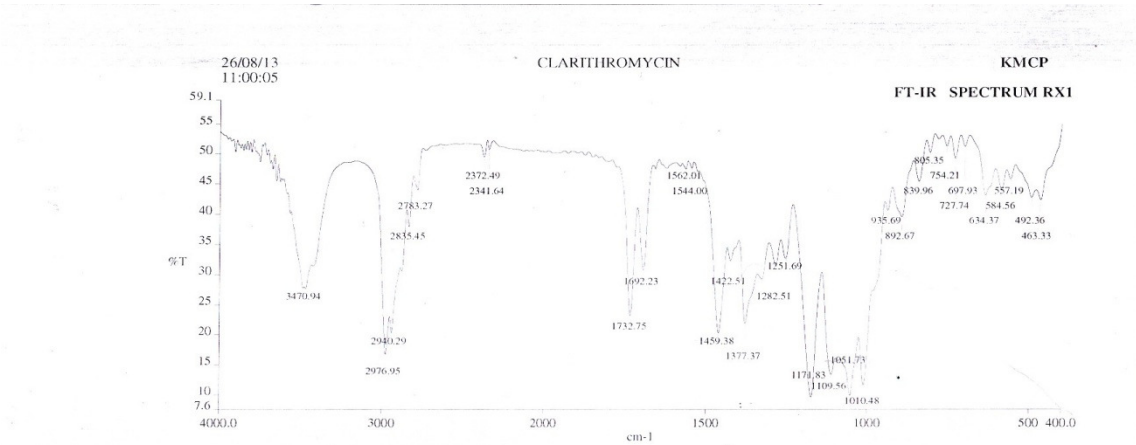
FTIR spectra data for mixture contain Clarithromycin, Aerosil & Ethyl cellulose were identified the wave number for group assigned in the infrared spectra shown in following table.14

Table No :14

IR spectral data of physical mixture of Clarithromycin, Aerosil & Ethyl cellulose

S.No	Frequency (cm^{-1})	Group Assigned
1	3467.26	O-H Stretching
2	2977.21	C-H Stretching
3	1734.10	C-O Stretching
4	1690.50	C=O Stretching
5	1377.73	C-N Stretching
6	1104.71	C-O-C Stretching
7	806.78	C-H deformation

Fig : 10 : IR Spectra of Clarithromycin

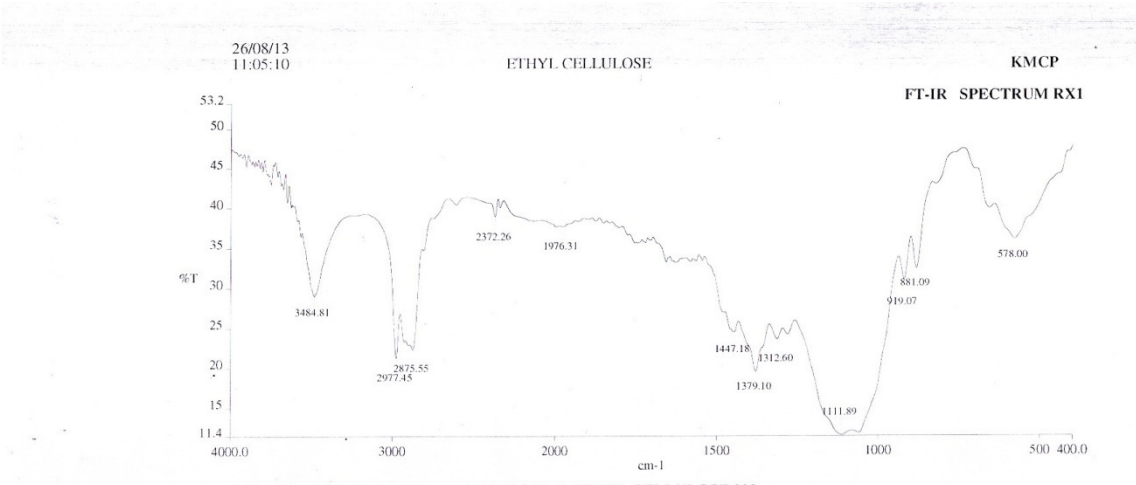


CLARITHROMYCIN.pk

CLARITHROMYCIN.002 3601 4000.00 400.00 9.62 54.95 4.00 %T 4 1.00

REF 4000 53.78 2000 50.32 600
3905.99 50.32 3855.98 50.59 3823.20 50.66 3805.53 50.31 3754.09 48.63
3677.47 47.42 3653.83 45.50 3470.94 27.70 2976.95 16.77 2940.29 20.36
2835.45 37.94 2783.27 44.03 2372.49 49.50 2341.64 50.78 1732.75 23.22
1692.23 30.77 1562.01 47.50 1544.00 47.64 1459.38 20.31 1422.51 32.25
1377.37 21.89 1282.51 31.54 1251.69 32.67 1171.83 9.61 1109.56 13.40

Fig : 11 : IR Spectra of Ethyl cellulose



ETHYL CELLULOSE.pk

ETHYL CELLULOSE.002 3601 4000.00 400.00 11.53 47.81 4.00 %T 4 1.00

REF 4000 47.46 2000 37.69 600
3906.30 45.23 3805.54 44.63 3754.50 42.96 3678.57 42.33 3653.60 40.73
3484.81 29.07 2977.45 21.29 2875.55 22.35 2372.26 38.95 1976.31 37.67
1447.18 24.48 1379.10 19.53 1312.60 23.63 1111.89 11.53 919.07 31.03
881.09 32.45 578.00 36.08

Fig : 12 : IR Spectra of Colloidal silicon dioxide (Aerosil)

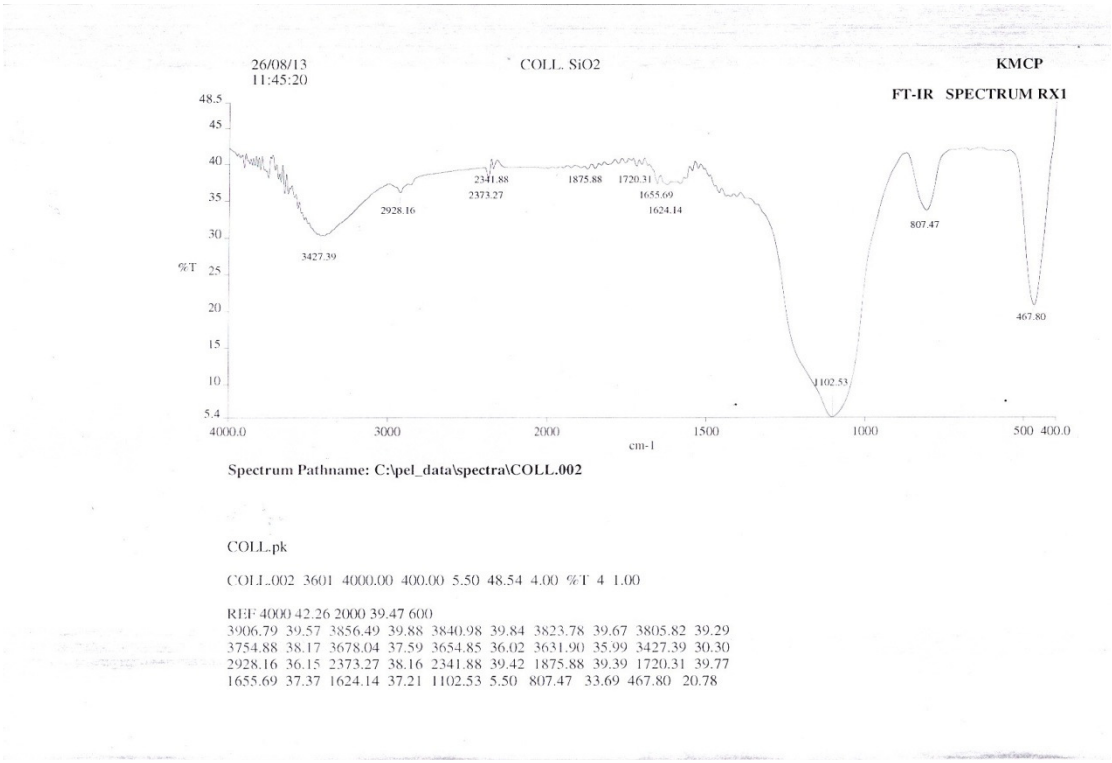


Fig : 13 : IR Spectra of mixture of Drug and Aerosil

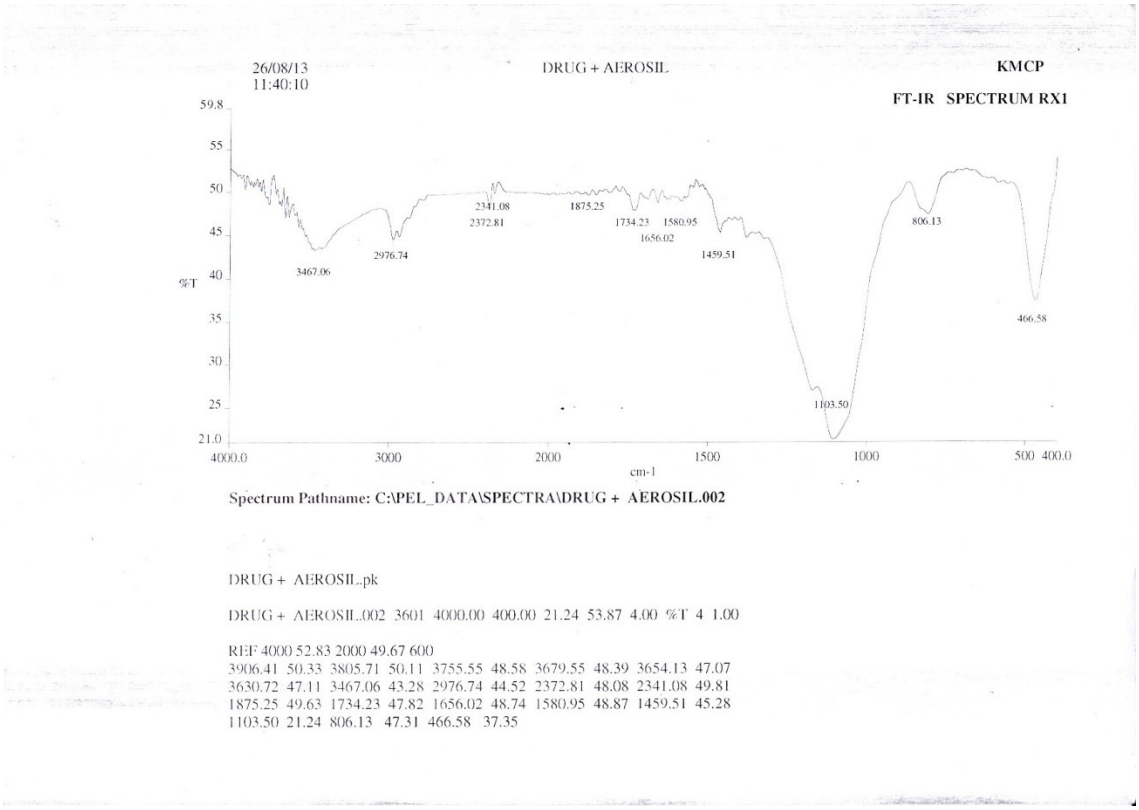
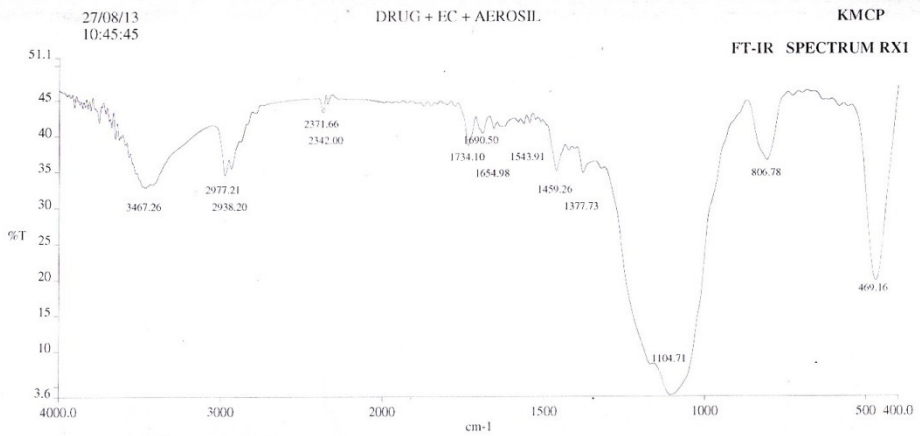


Fig : 14 : IR Spectra of mixture of Drug, Aerosil & Ethyl cellulose



Spectrum Pathname: C:\PEL_DATA\SPECTRA\DRUG + EC + AE.002

DRUG + EC + AE.pk

DRUG + EC + AE.002 3601 4000.00 400.00 3.74 46.98 4.00 %T 4 1.00

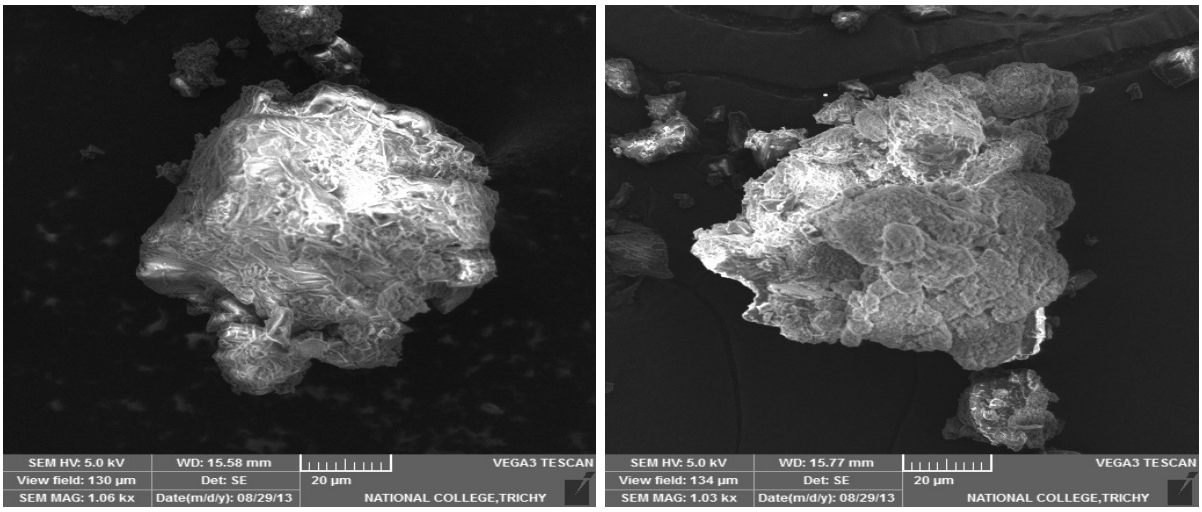
REF 4000 46.46 2000 44.68 600
3905.58 44.05 3855.67 43.91 3822.82 43.86 3805.16 43.62 3753.29 41.89
3677.18 41.23 3652.89 39.63 3467.26 32.78 2977.21 34.53 2938.20 35.47
2371.66 43.28 2342.00 44.54 1734.10 38.64 1690.50 40.35 1654.98 40.94
1543.91 41.87 1459.26 34.97 1377.73 34.86 1104.71 3.74 806.78 36.58
469.16 19.81

EVALUATION OF CLARITHROMYCIN MICROPARTICLE

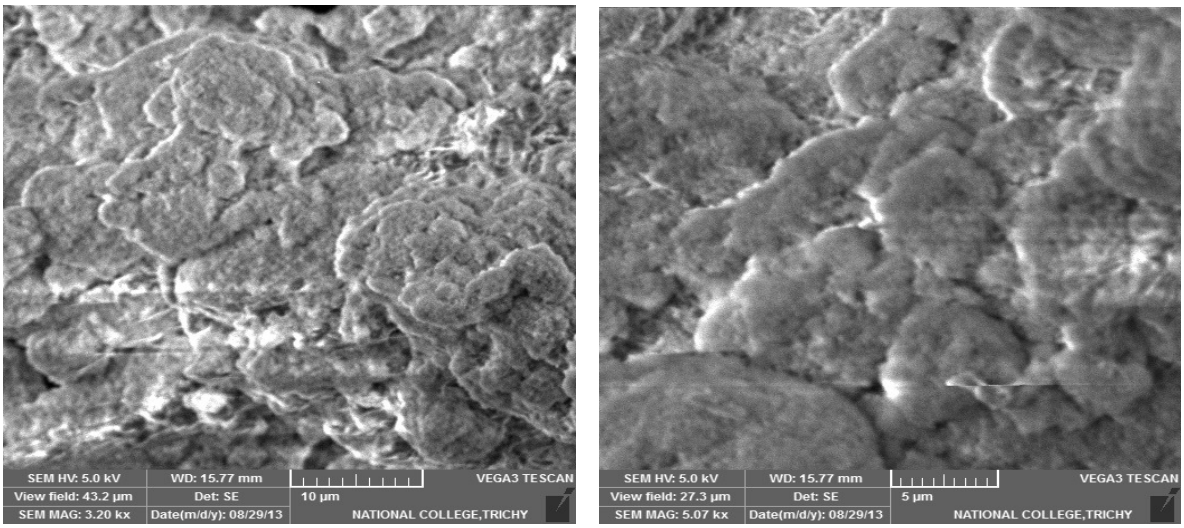
Scanning electron microscopy (SEM)

Morphology of microparticle was examined by scanning electron microscopy. The view of the microparticle showed an irregular structure with a moderately smooth surface morphology. Scanning electron microphotographs of floating microparticle of Clarithromycin are shown in figure 15

Fig No 15: Scanning electron microphotograph of floating microparticles of Clarithromycin.



(a) (b)



(c) (d)

Micromeritic properties

The microparticles were characterized by their micromeritic properties such as particle size, bulk density, tapped density, compressibility index and angle of repose. The particle size was measured by sieve analysis. The results are given in Table (15, 16) & Fig (16, 17). The flow properties are expressed in terms of Carr's index. The value of bulk density, tapped density, compressibility index and angle of repose are given in Table (17, 18).

Table 15: Mean particle size of of floating microparticles of Clarithromycin using Dichloromethane as solvent

Formulation code	particle size (mean±sd) n=3 (mcg)
F1	266.07±1.25
F2	291.01±2.36
F3	302.77±2.68
F4	308.86±1.69
F5	312.71±3.25
F6	317.84±2.95

Fig No.16: Comparison of average particle size of floating microparticle of Clarithromycin using Dichloromethane as solvent

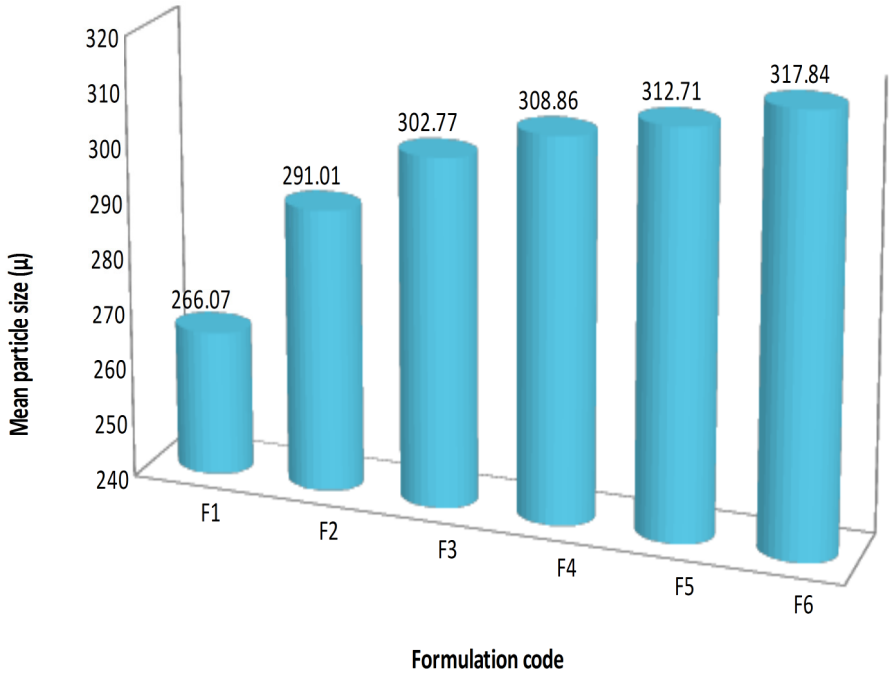


Table 16: Mean particle size of of floating microparticle of Clarithromycin using Ethanol as solvent

Formulation code	particle size (mean±sd) n=3
F7	270.49±2.32
F8	302.52±1.65
F9	313.07±3.54
F10	317.82±3.25
F11	321.26±1.25
F12	325.27±2.78

Fig No.17: Comparison of average particle size of floating microparticle of Clarithromycin using Ethanol as solvent

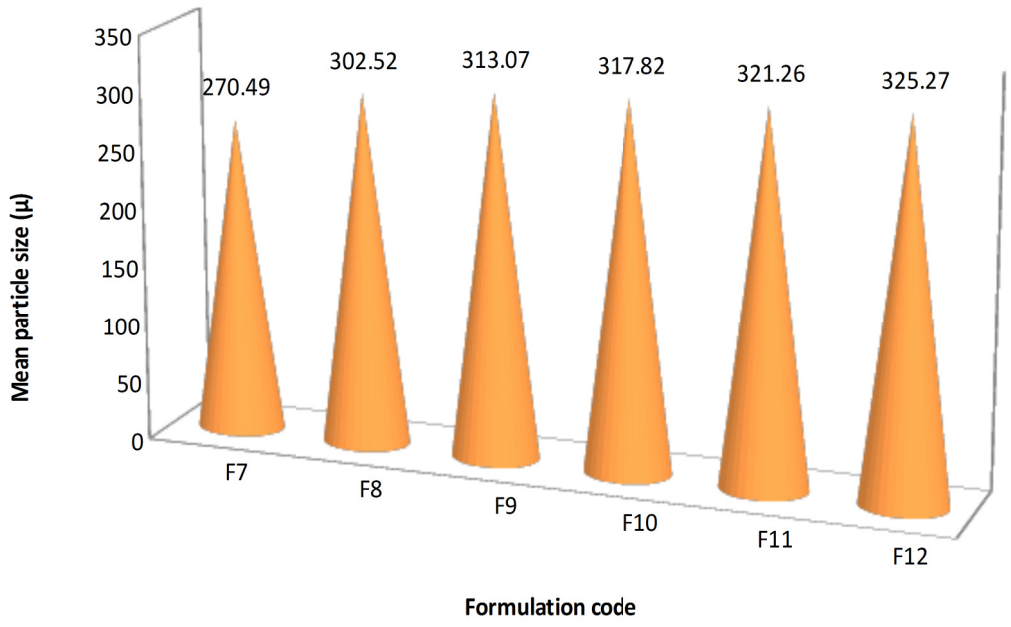


Table 17: Micromeritic property of floating microparticles of Clarithromycin using Dichloromethane as solvent

Formulation Code	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carrs Index	Hausners ratio	Angle of Repose
F1	0.442	0.486	9.05	1.10	$29^0.32'$
F2	0.441	0.539	18.18	1.22	$37^0.40'$
F3	0.483	0.590	18.14	1.22	$36^0.42'$
F4	0.510	0.611	16.53	1.20	$35^0.31'$
F5	0.552	0.651	15.21	1.18	$35^0.24'$
F6	0.610	0.714	14.57	1.17	$34^0.10'$

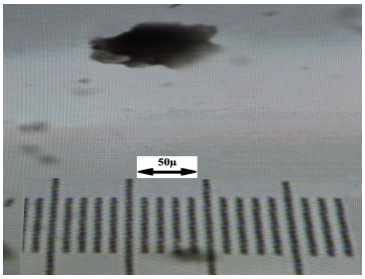
Table 18: Micromeritic property of floating microparticle of Clarithromycin using Ethanol as solvent

Formulation Code	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carrs Index	Hausners ratio	Angle of Repose
F7	0.412	0.450	8.4	1.09	$27^0.15'$
F8	0.333	0.408	18.38	1.23	$34^0.20'$
F9	0.374	0.452	17.26	1.21	$33^0.15'$
F10	0.404	0.482	16.18	1.19	$33^0.01'$
F11	0.451	0.538	16.17	1.19	$32^0.46'$
F12	0.494	0.572	13.64	1.16	$31^0.22'$

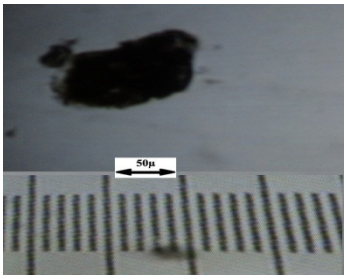
Optical microscopy

Determination of average particle size of Clarithromycin floating microparticles was carried out by Optical microscopy in which stage micrometer was employed. Phase contrast microscope was used here. The results are given in the fig no (18, 19).

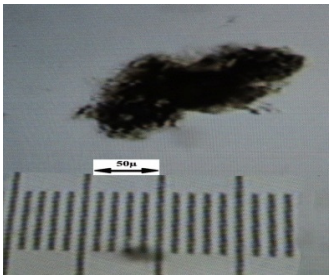
Fig No.18 Microscopic image showing microparticles of Clarithromycin formulation (a) F1 (b) F2 (c) F3 (d)F4 (e)F5 (f)F6



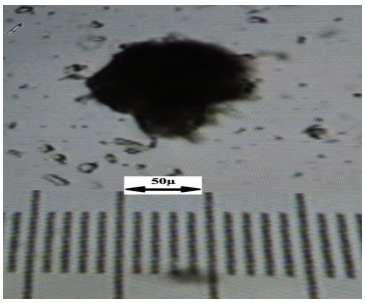
F1



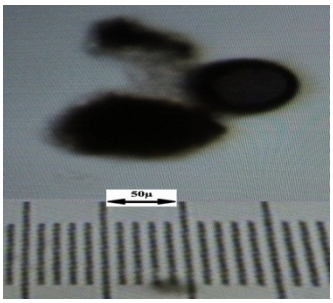
F2



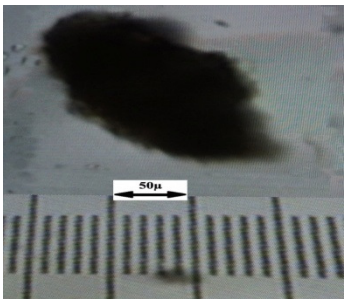
F3



F4

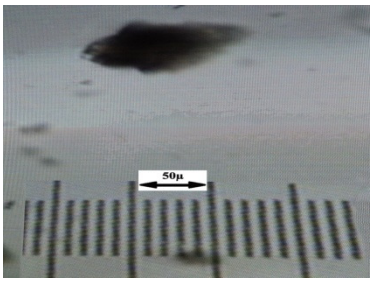


F5

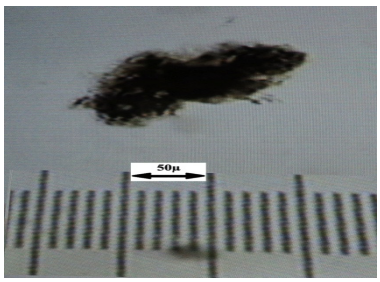


F6

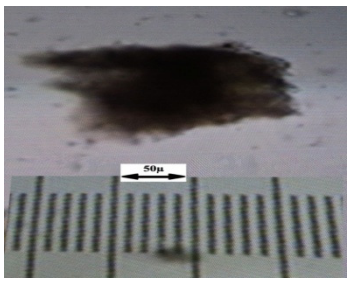
Fig No.19 Microscopic image showing microparticles of Clarithromycin formulation (a) F7 (b) F8 (c) F9 (d)F10 (e)F11 (f)F12.



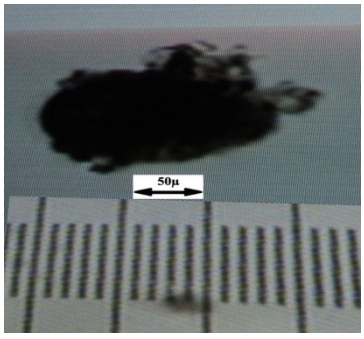
F7



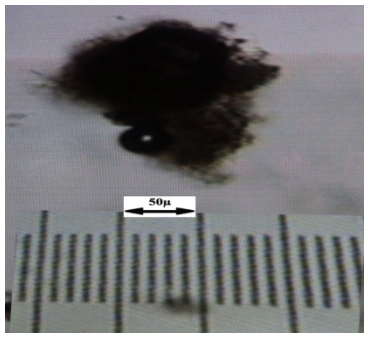
F8



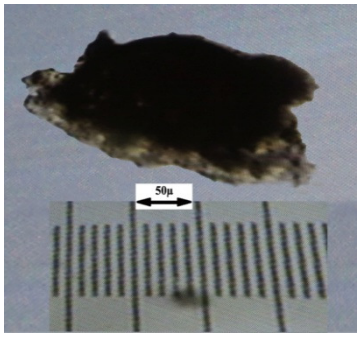
F9



F10



F11



F12

Percent yield of microparticles

The yields of preparation of Clarithromycin microparticles are high for all microparticles obtained which are about 90%. It shows that the recovery of the material is good which is significant from the economical view. The results are given in Table (19, 20) & Fig (20, 21).

Table 19: Percentage yield of of floating microparticle of Clarithromycin using Dichloromethane as solvent

Formulation code	Percentage yield (%)
F1	92.73
F2	93.45
F3	94.36
F4	96.00
F5	96.73
F6	97.82

Figure 20:Comparison of Percentage yield of of floating microparticle of Clarithromycin using Dichloromethane as solvent

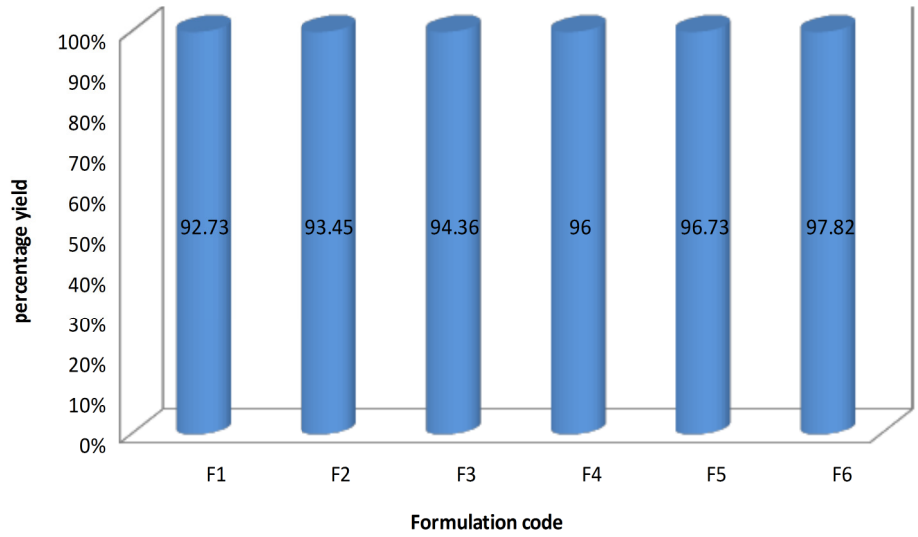
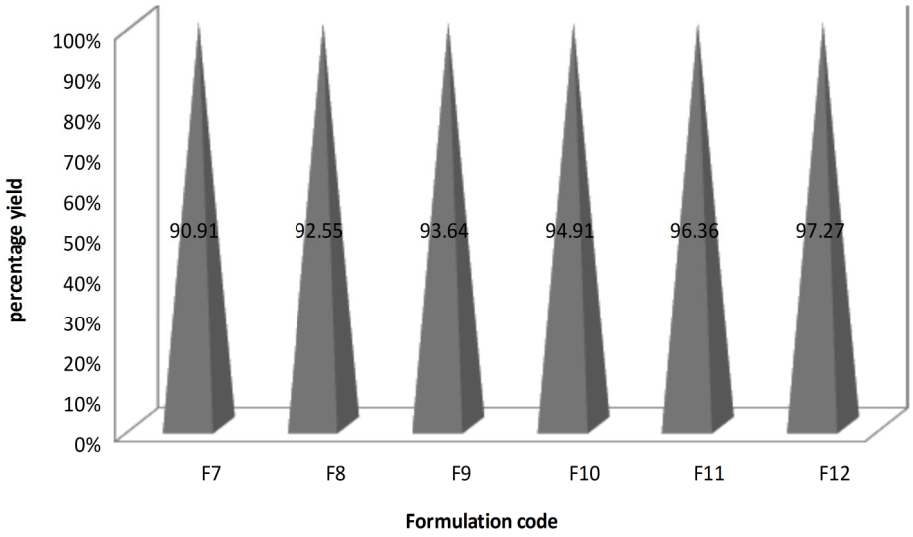


Table :20 Percentage yield of of floating microparticle of Clarithromycin using Ethanol as solvent

Formulation code	Percentage yield (%)
F7	90.91
F8	92.55
F9	93.64
F10	94.91
F11	96.36
F12	97.27

Figure No.21:Comparison of Percentage yield of of floating microparticle of Clarithromycin using Ethanol as solvent



***In-vitro* Buoyancy**

The buoyancy test was carried out to investigate the floatability of prepared microparticles. The results showed a tendency that the larger the particle size, the longer floating time. The results are given in Table (21, 22) & Fig No (22-27).

Table 21 : *Invitro* Buoyancy of of floating microparticle of Clarithromycin using Dichloromethane as solvent

Formulation code	*Invitro* Buoyancy (%)
F1	70.34
F2	78.45
F3	80.81
F4	82.37
F5	88.31
F6	92.12

Figure 22:Comparison of *Invitro* Buoyancy of of floating microparticle of Clarithromycin using Dichloromethane as solvent

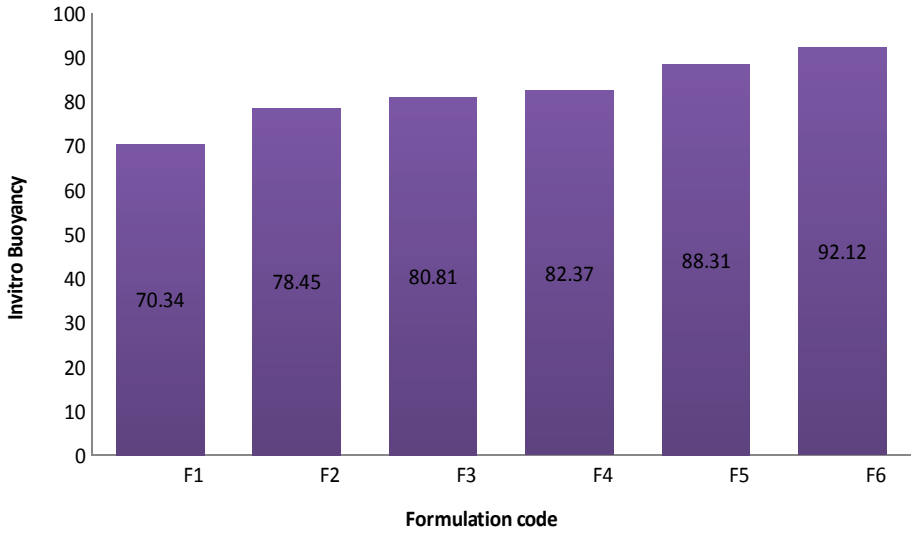


Table 22 : *Invitro* Buoyancy of of floating microparticle of Clarithromycin using Ethanol as solvent

Formulation code	Invitro Buoyancy (%)
F7	69.86
F8	76.31
F9	79.43
F10	80.97
F11	86.48
F12	91.87

Figure No 23 :Comparison of *Invitro* Buoyancy of of floating microparticle of Clarithromycin using Ethanol as solvent

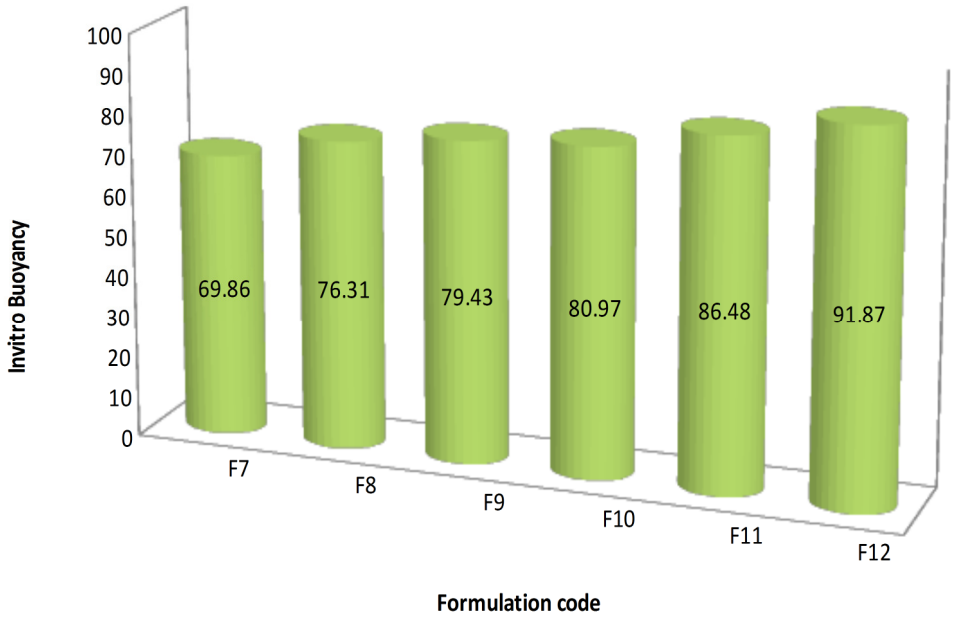


Fig No.24 : In-vitro buoyancy of floating microparticles of Clarithromycin formulation (a)F1,(b)F2,(c)F3.

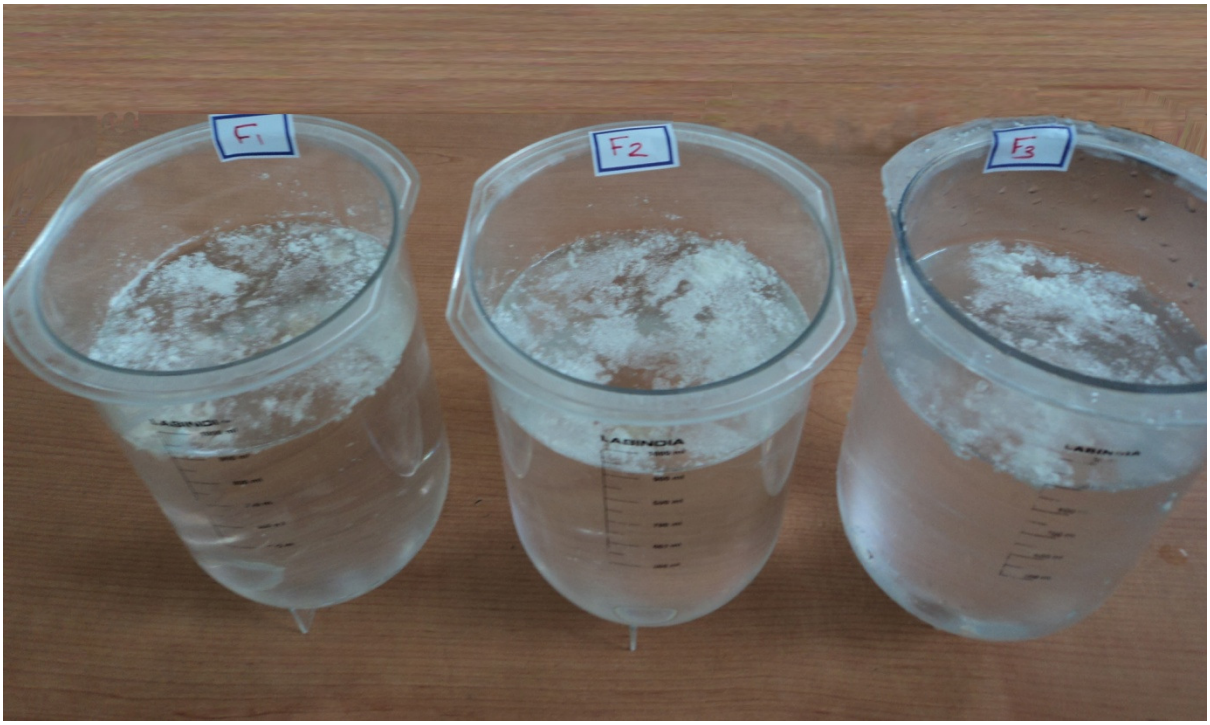


Fig No.25 : In-vitro buoyancy of floating microparticles of Clarithromycin formulation (a)F4, (b)F5,(c)F6

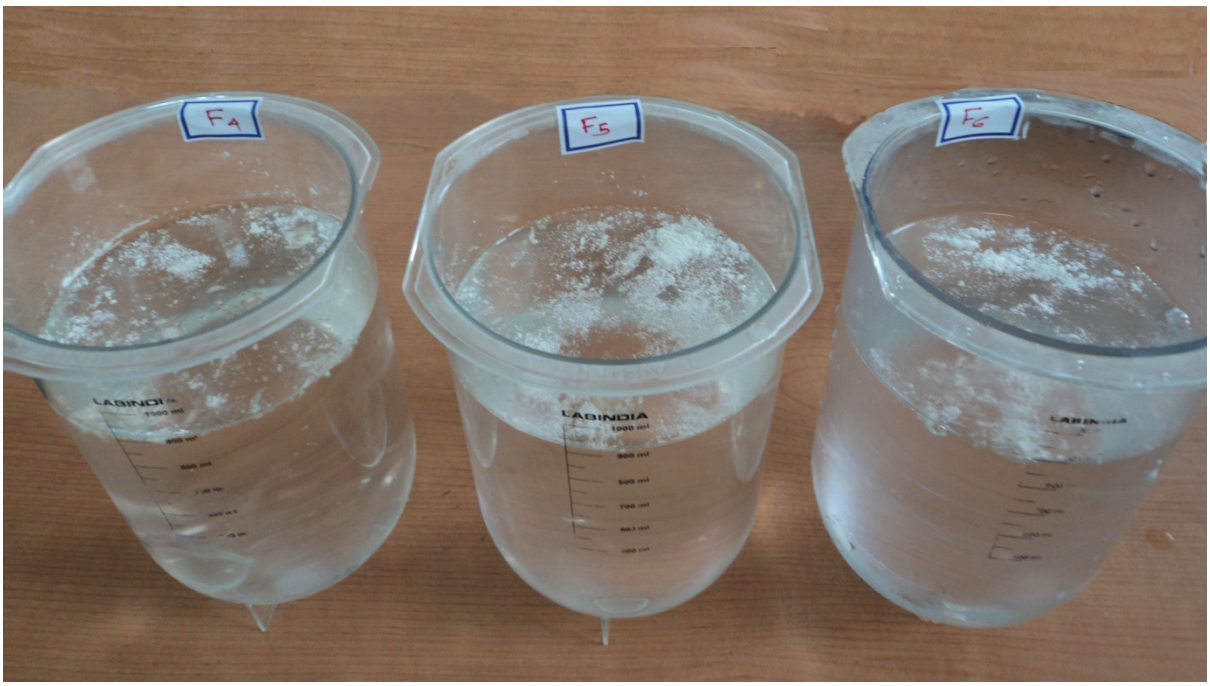


Fig No.26 : In-vitro buoyancy of floating microparticles of Clarithromycin formulation (a)F7,(b)F8,(c)F9

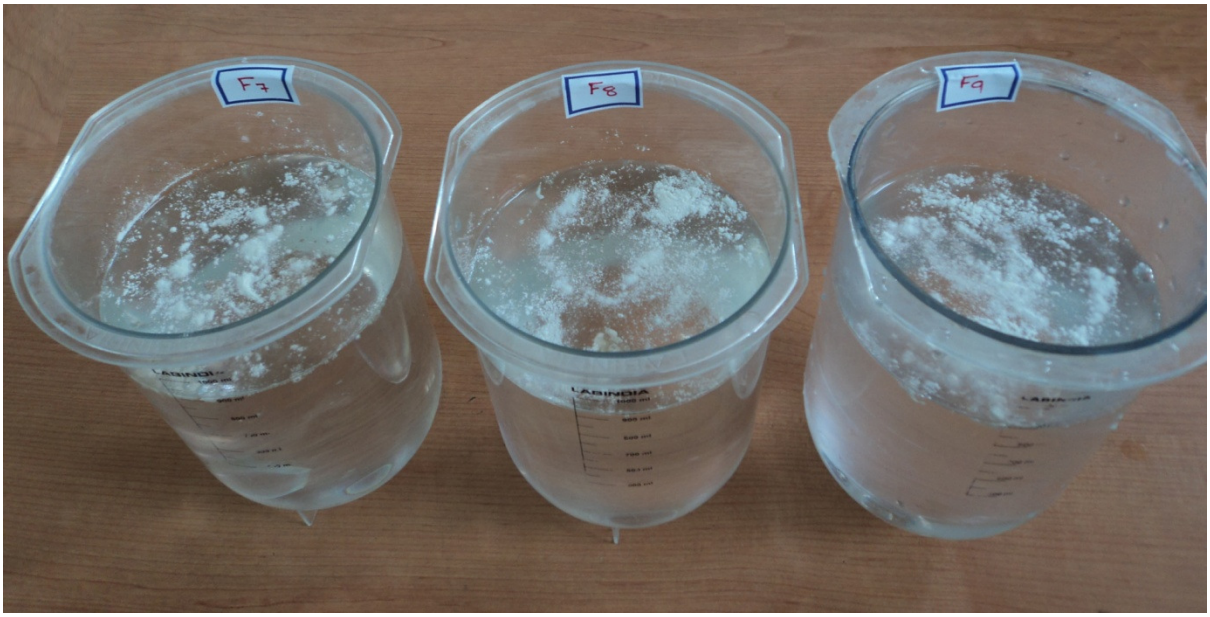
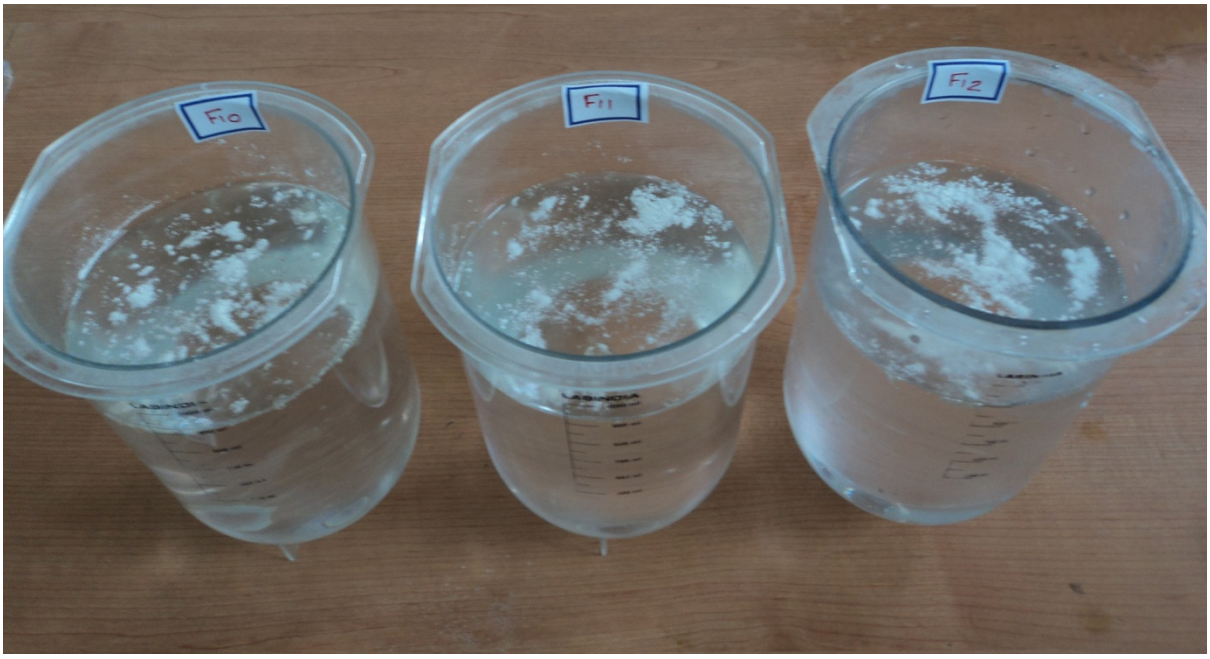


Fig No.27 : In-vitro buoyancy of floating microparticles of Clarithromycin formulation (a)F10,(b)F11,(c)F12



Incorporation efficiency

The incorporation efficiency was found to be good in all the prepared formulation. Results demonstrated that increase in concentration of ethyl cellulose, increased the entrapment of the drug. The results are given in the Table (23, 24) & Fig No (28, 29).

Table 23 : Incorporation Efficiency of of floating microparticle of Clarithromycin using Dichloromethane as solvent

Formulation code	Incorporation Efficiency
F1	91.22
F2	92.24
F3	93.98
F4	95.42
F5	95.99
F6	96.87

Figure No.28:Comparison of Incorporation Efficiency of of floating microparticle of Clarithromycin using Dichloromethane as solvent

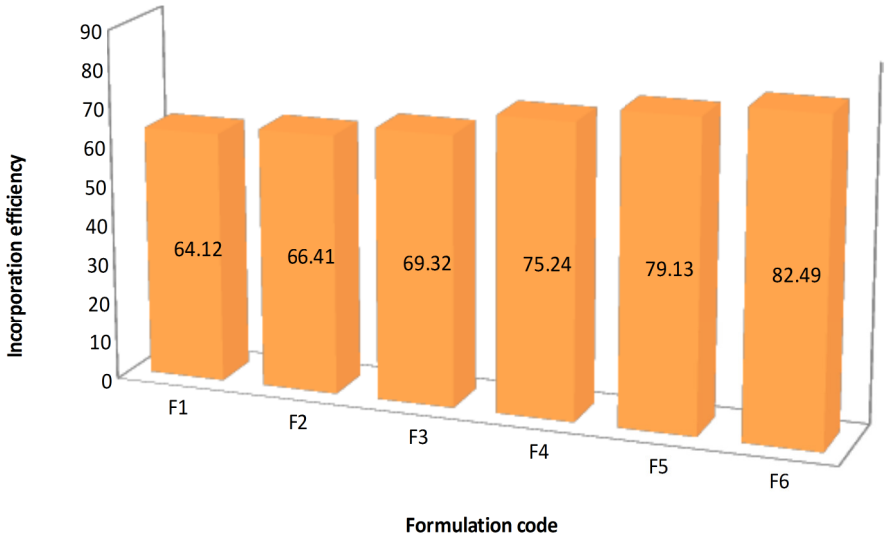
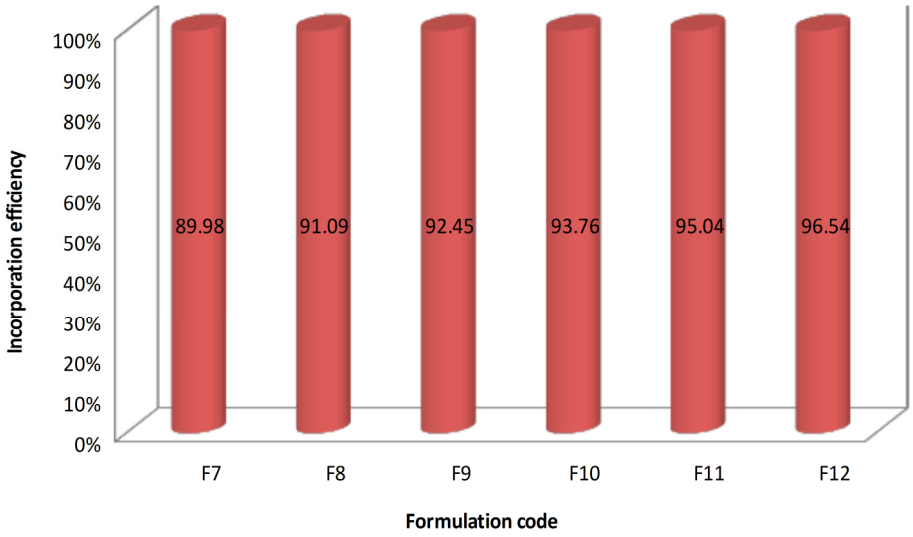


Table 24: Incorporation Efficiency of of floating microparticle of Clarithromycin using Ethanol as solvent

Formulation code	Incorporation Efficiency
F7	89.98
F8	91.09
F9	92.45
F10	93.76
F11	95.04
F12	96.54

Figure No.29:Comparison of Incorporation Efficiency of of floating microparticle of Clarithromycin using Ethanol as solvent



Crushing strength

Crushing strength of Clarithromycin from floating microparticles were performed using T.A.X.T plus Texture Analyser. Results demonstrated that increase in concentration of

ethyl cellulose, increased crushing strength of the microparticle. The results are given in the Table. 25 & Fig (30, 31).

Table no : 25 Crushing strength of F1-F12

S.No	Formulation code	Crushing strength N
1	F1	50.579
2	F2	54.921
3	F3	44.549
4	F4	48.807
5	F5	74.354
6	F6	101.987
7	F7	7.947
8	F8	5.814
9	F9	11.758
10	F10	49.255
11	F11	79.206
12	F12	109.069

Figure No.30: The crushing strength of F1-F6.

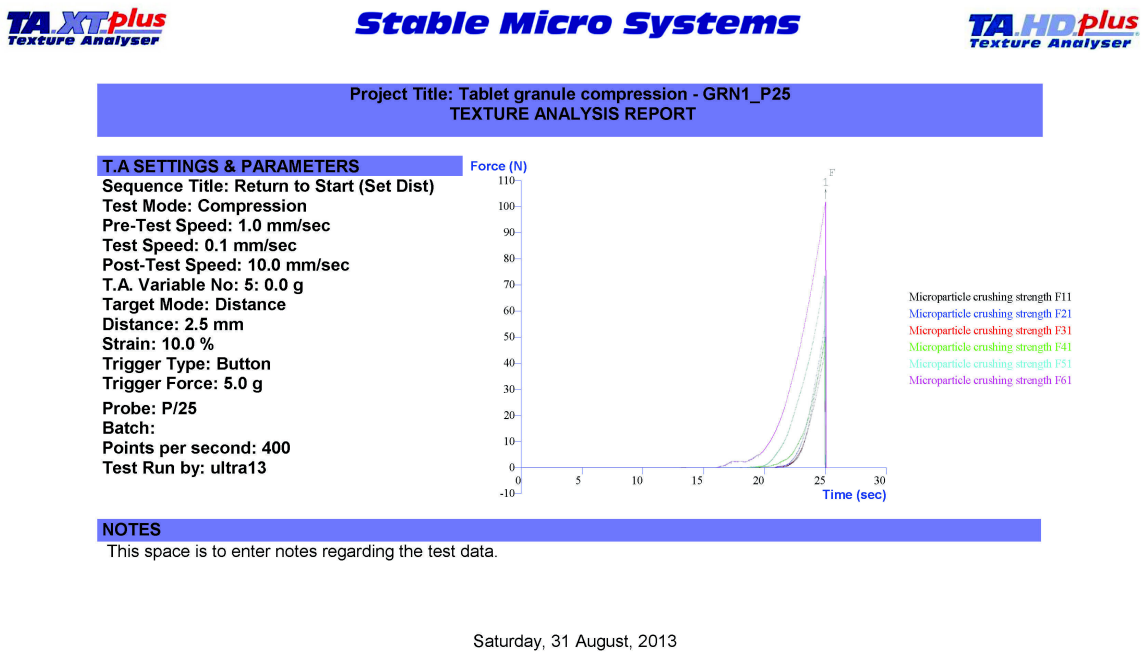
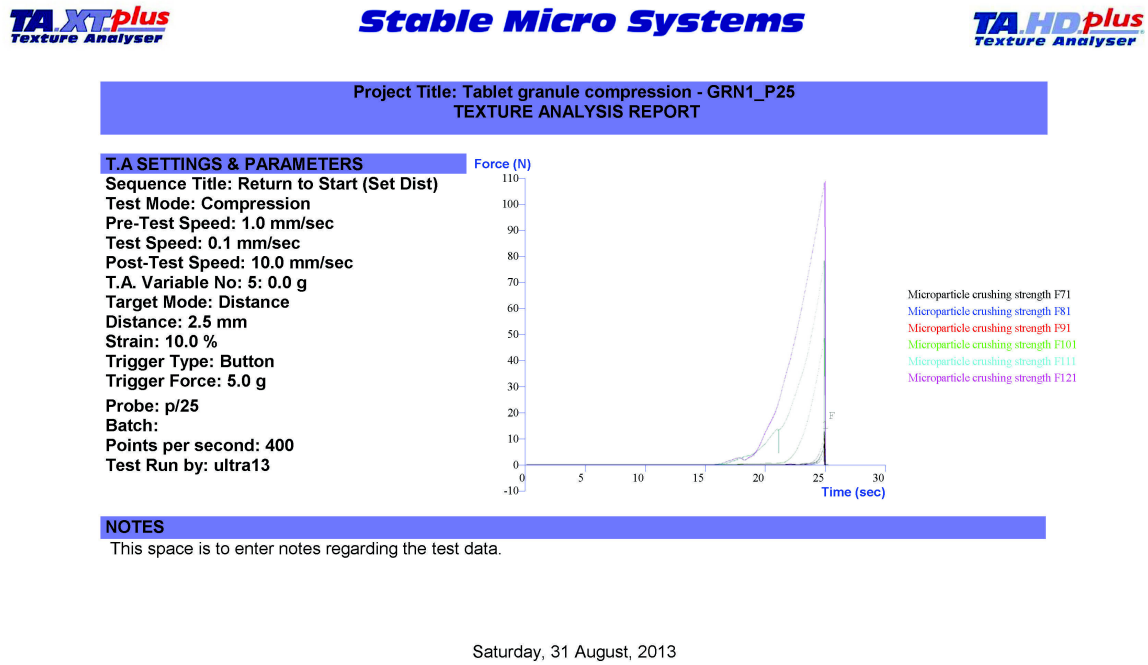


Figure No.31: The crushing strength of F7-F12.



In-vitro drug release studies

The dissolution study was carried out for 3 hours for all formulation. The drug released study was carried out by using USP type 2 dissolution test apparatus. Microparticles were studied at Potassium dihydrogen ortho phosphate buffer Ph 4.4. The Clarithromycin microparticles were analysed for *in-vivo* drug release estimation the result given in the table no:(26-37). Among all formulations, F2 was found to be the best formulation as it release Clarithromycin 98.07% in a sustained manner with constant fashion over extended period of time. The Clarithromycin microparticles were analysed for *in-vitro* drug release estimation the result given in the table no: (26-37) & fig no (32-45)

Table No:26

IN-VITRO DRUG RELEASE DATA FOR F1

S.No	Time in min	Cumulative % drug release
1	0	0
2	30	5.25
3	60	13.5
4	90	24
5	120	36
6	180	47.25

Fig No;32 IN-VITRO DRUG RELEASE GRAPH OF F1

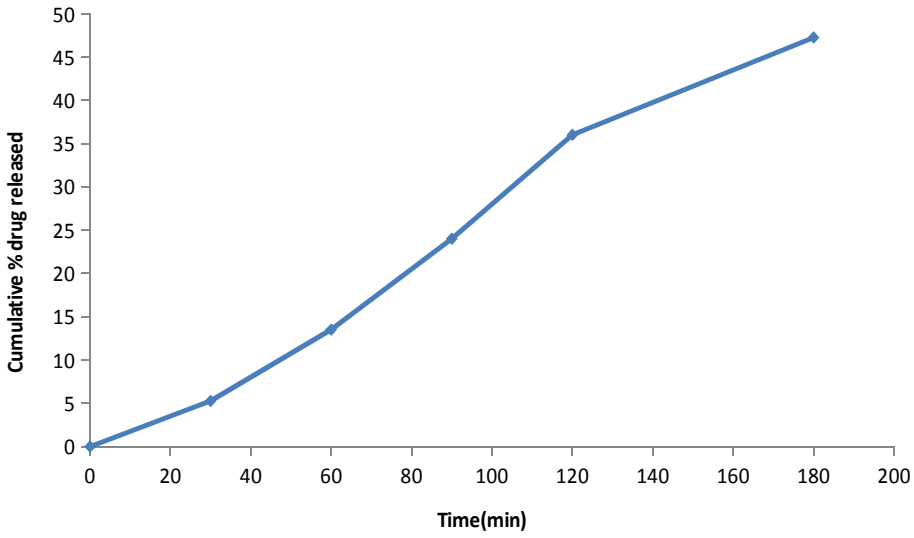


Table no :27

IN-VITRO DRUG RELEASE DATA FOR F2

S.No	Time in min	Cumulative % drug release
1	0	0
2	30	24.08
3	60	40.89
4	90	60.46
5	120	80.84
6	180	98.07

No:33 IN-VITRO DRUG RELEASE GRAPH OF F2

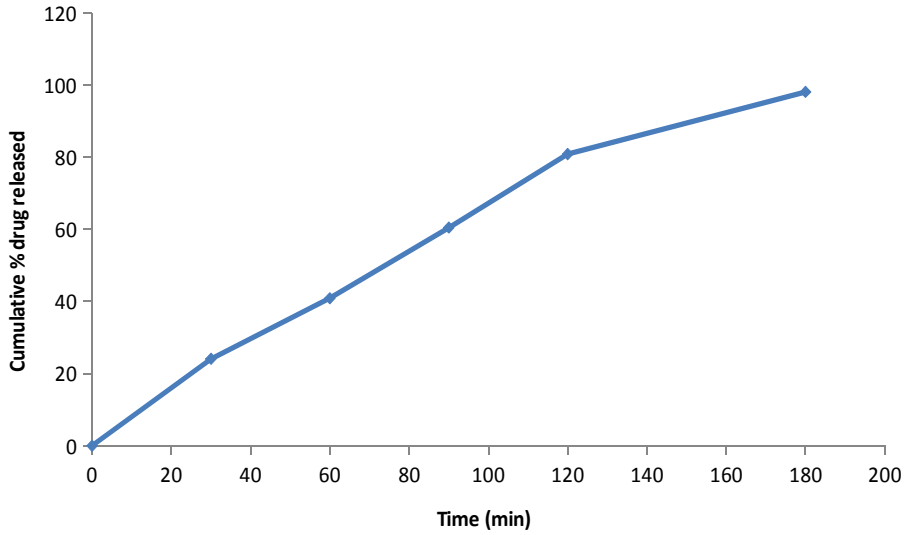


Table No:28

IN-VITRO DRUG RELEASE DATA FOR F3

S.No	Time in min	Cumulative % drug release
1	0	0
2	30	19.08
3	60	31.33
4	90	39.45
5	120	66.89
6	180	88.01

No:34 IN-VITRO DRUG RELEASE GRAPH OF F3

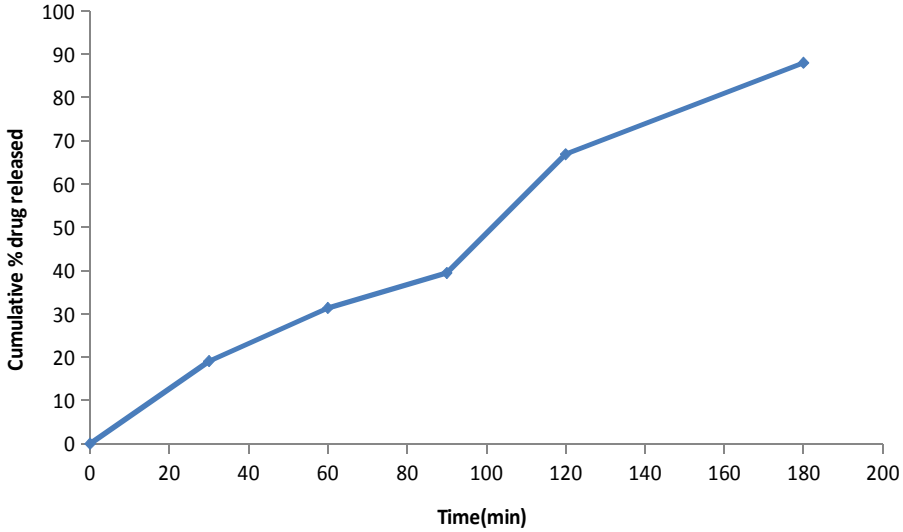


Table No.29

IN-VITRO DRUG RELEASE DATA FOR F4

S.No	Time in min	Cumulative % drug release
1	0	0
2	30	16.50
3	60	28.50
4	90	30.75
5	120	60
6	180	82.50

Fig No:35 IN-VITRO DRUG RELEASE GRAPH OF F4

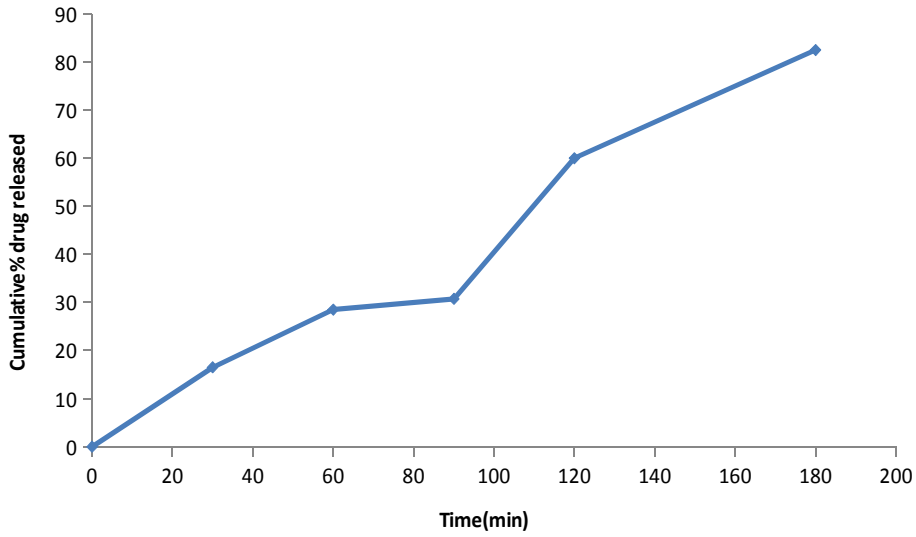


Table No:30

IN-VITRO DRUG RELEASE DATA FOR F5

S.No	Time in min	Cumulative % drug release

1	0	0
2	30	11.25
3	60	19.50
4	90	28.50
5	120	42.75
6	180	67.5

Fig No:36 IN-VITRO DRUG RELEASE GRAPH OF F5

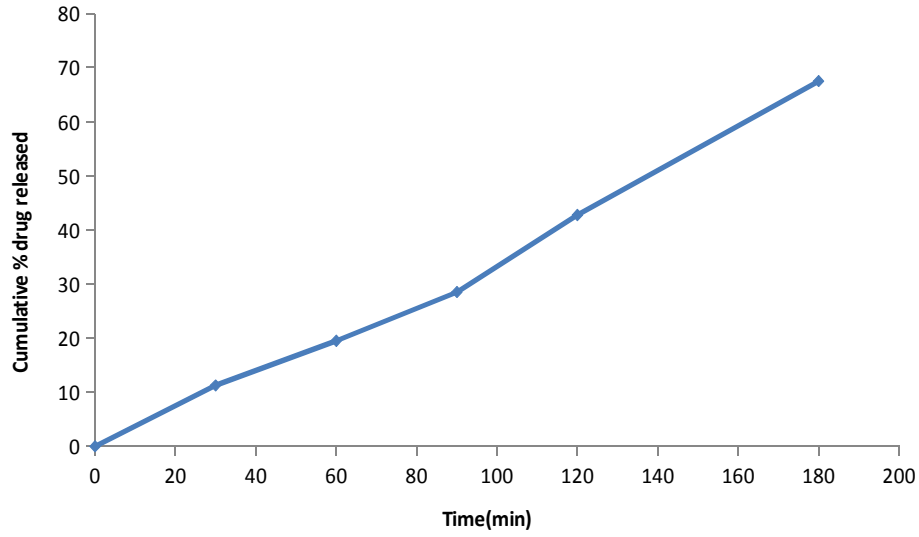


Table No:31

IN-VITRO DRUG RELEASE DATA FOR F6

S.No	Time in min	Cumulative % drug release

1	0	0
2	30	5.25
3	60	8.26
4	90	29.25
5	120	47.25
6	180	54.75

Fig No:37 IN-VITRO DRUG RELEASE GRAPH OF F6

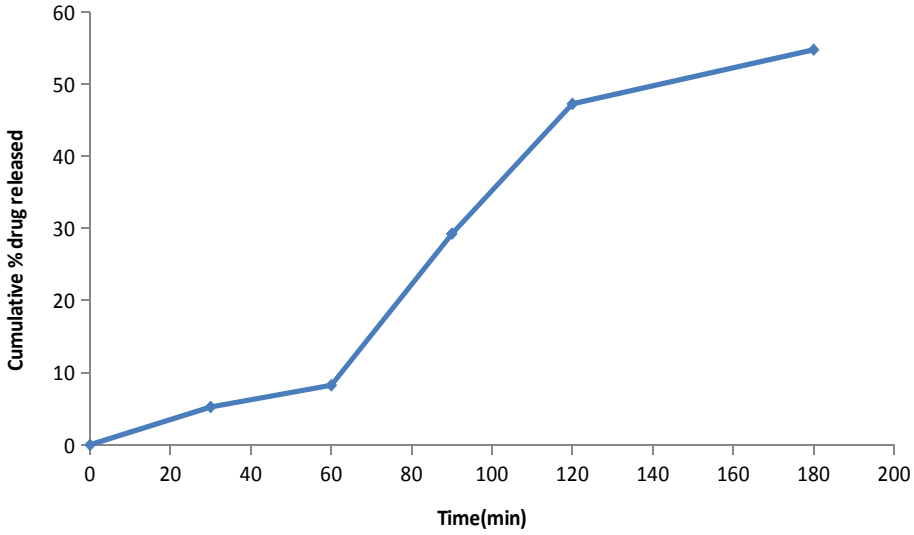


Table No:32

IN-VITRO DRUG RELEASE DATA FOR F7

S.No	Time in min	Cumulative % drug release
1	0	0

2	30	12.27
3	60	26.28
4	90	38.22
5	120	48.07
6	180	64.08

Fig: 38 IN-VITRO DRUG RELEASE GRAPH OF F7

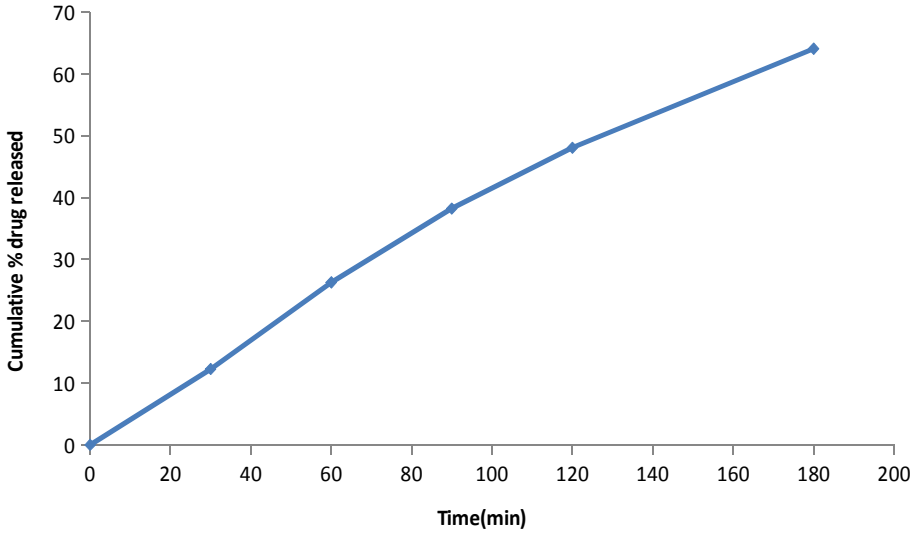


Table No:33

IN-VITRO DRUG RELEASE DATA FOR F8

S.No	Time in min	Cumulative % drug release
1	0	0
2	30	20.86

3	60	38.86
4	90	52.9
5	120	76.48
6	180	94.02

Fig:39 IN-VITRO DRUG RELEASE GRAPH OF F8

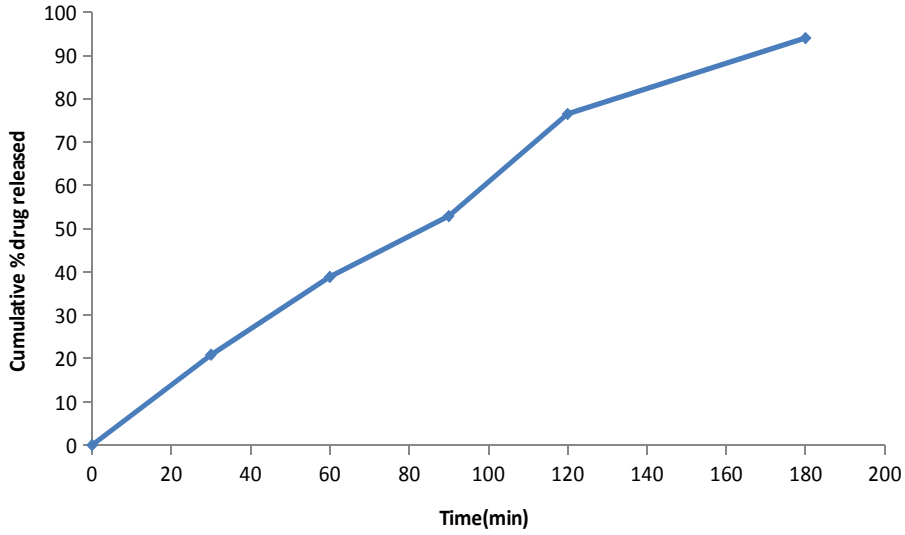


Table No:34

IN-VITRO DRUG RELEASE DATA FOR F9

S.No	Time in min	Cumulative % drug release
1	0	0
2	30	18.05
3	60	34.07

4	90	46.02
5	120	70.82
6	180	84.17

Fig :40 IN-VITRO DRUG RELEASE GRAPH OF F9

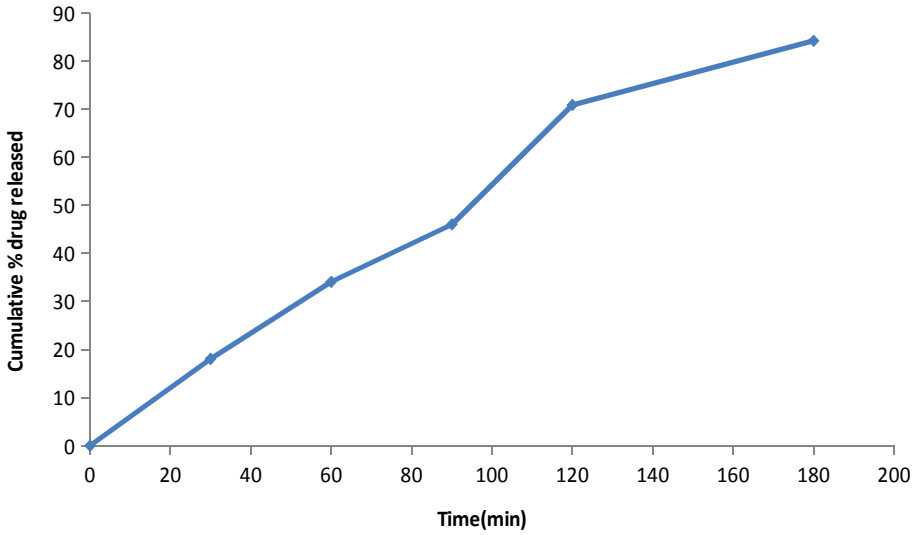


Table :35

IN-VITRO DRUG RELEASE DATA FOR F10

S.No	Time in min	Cumulative % drug release
1	0	0
2	30	15.83
3	60	31.29
4	90	42.06

5	120	66.65
6	180	78.08

Fig: 41 IN-VITRO DRUG RELEASE GRAPH OF F10

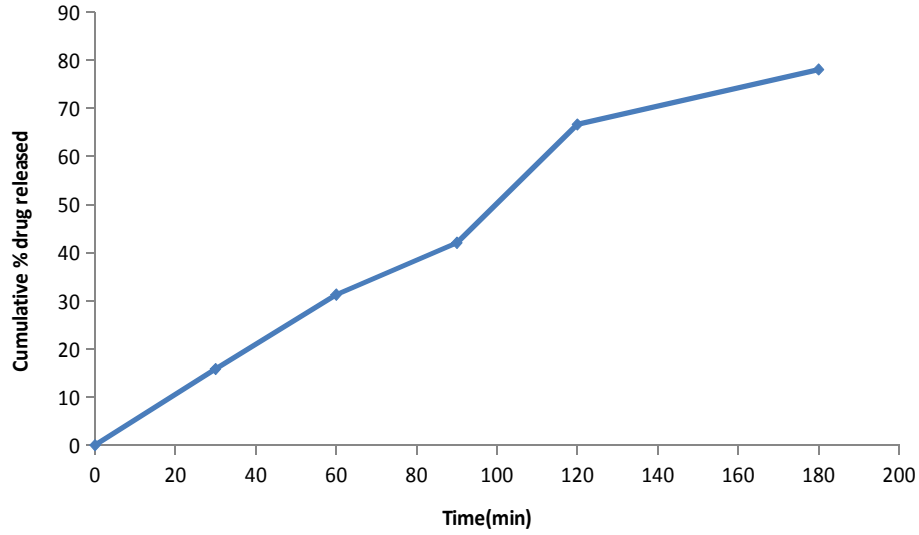


Table No:36

IN-VITRO DRUG RELEASE DATA FOR F11

S.No	Time in min	Cumulative % drug release
1	0	0
2	30	13.20
3	60	27.02
4	90	38.69
5	120	56.42
6	180	64.08

Fig: 42 IN-VITRO DRUG RELEASE GRAPH OF F11

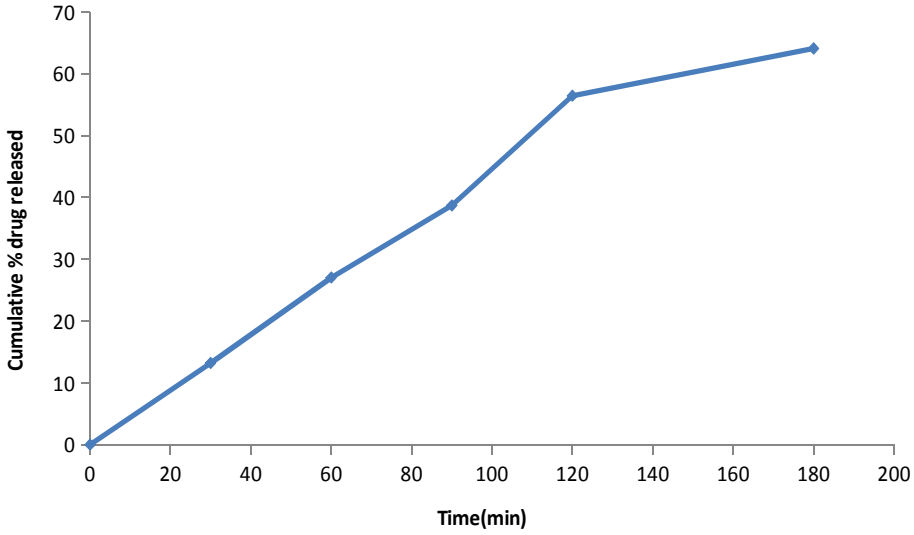


Table No: 37

IN-VITRO DRUG RELEASE DATA FOR F12

S.No	Time in min	Cumulative % drug release
1	0	0
2	30	10.25
3	60	22.47
4	90	34.42
5	120	40.86
6	180	48.65

Fig:43 IN-VITRO DRUG RELEASE GRAPH OF F12

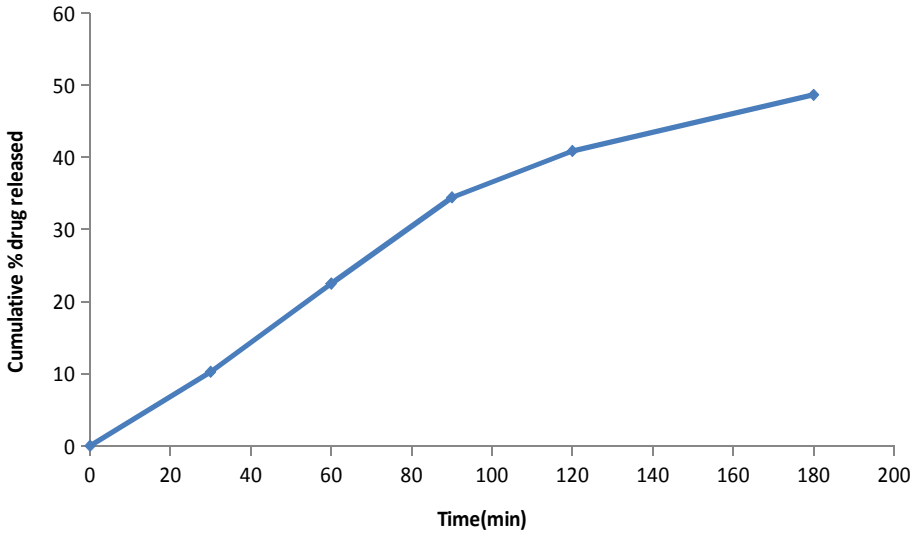


Fig No: 44 *Invitro* drug release comparison data for F1, F2, F3, F4, F5, F6.

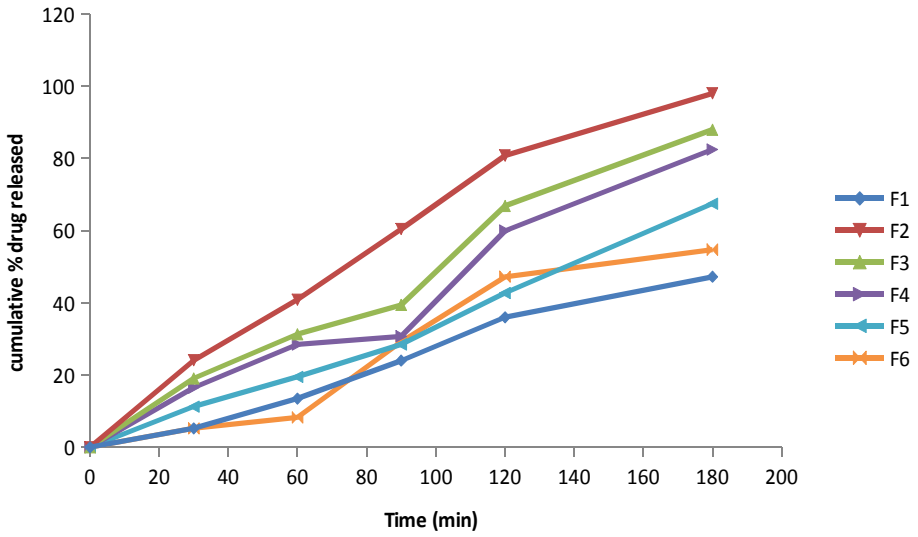
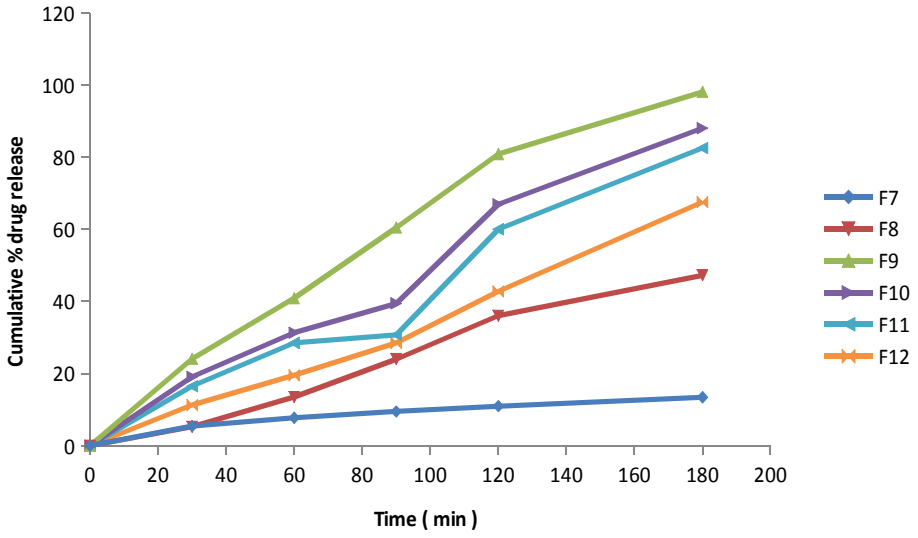


Fig No: 45 *Invitro* drug release comparison data for F7, F8, F9, F10, F11, F12.



Study of drug release kinetics

In order to find out the drug release and mechanism, the *invitro* release data subjected to the different mode of graphical treatment.

1. The percentage cumulative drug release Vs Time.

2. The cumulative percent drug remaining Vs Time.

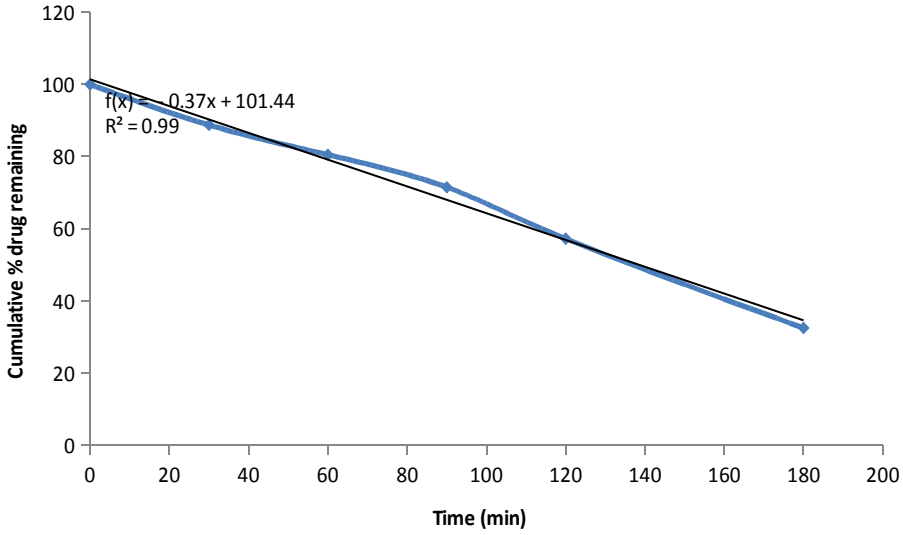
The release mechanism of Clarithromycin from various formulations was determined by comparing their respective correlation coefficient[13]. The results are shown in Table.38 & Fig 46.

Table: 38

Kinetic analysis of release data for Hixson Crowell model

Batch No	Regression coefficient (R^2)
F1	0.984
F2	0.971
F3	0.981
F4	0.968
F5	0.992
F6	0.925
F7	0.986
F8	0.978
F9	0.971
F10	0.968
F11	0.958
F12	0.946

Fig:46 Hixson Crowell model for Batch-F5


120
100
80
60
40
20
0
f(x) = −0.37x + 101.44
R² = 0.99
Cumulative % drug remaining
0
20
40
60
80
100
120
140
160
180
200
Time (min)

DISCUSSION

Floating drug delivery systems remain buoyant in the stomach as they have a bulk density less than gastric fluids and thus prolonging the stay of the dosage form in stomach. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from stomach. This results in an increased gastric residence time and a better control of the fluctuation in plasma drug concentration. Single unit formulations (floating tablet) are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. On the other hand a floating system made of multiple unit forms (floating microparticles) has relative merits compared to a single unit preparation. Floating microparticles provide a constant and prolonged therapeutic effect which will reduce dosing frequency[27].

Floating multiparticulate dosage form have been prepared by solvent diffusion and solvent evaporation method to create an hollow inert core [26, 27]. Porous calcium pectinate beads with bulk density less than 1 were prepared by Badve SS[39]. Alternatevely floating microparticles based on low density foam powder were prepared with polypropylene foam powder, matrix forming polymer and the drug (Verapamil HCL)[28]. Instead of foam powder highly porous carrier material like calcium silicate was used along with Eudragit S to deliver Repaglinide over an extend period of time. In the present study, colloidal silicon dioxide (Aerosil) was used as the porous material. Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying[29].

The aim of present study was to develop floating microparticles of Clarithromycin by using ethyl cellulose as matrix material and colloidal silicon dioxide (Aerosil) as the porous material. Calibration curve for the estimation of Clarithromycin was constructed by a colorimetric method which obeyed Beer's Lambert law in the range of 20-100 mcg/ml.

Infrared spectroscopy

Drug- excipient compatibility was assessed by FTIR spectroscopy to find out any chemical interaction between Clarithromycin and excipients used. The FTIR spectra of Clarithromycin, polymer (ethyl cellulose) and selected formulations as shown in the figure(10-14) revealed the same transmittance pattern for the drug, drug with polymer and

drug, ethyl cellulose and colloidal silicon dioxide. Hence further formulation studies were extended.

Preparation of microparticles

Totally 12 formulations are prepared. Clarithromycin floating microparticle formulation F1 to F6 containing ethyl cellulose using dichloromethane as solvent and formulation F7 to F12 containing ethyl cellulose using ethanol as solvent.

Scanning electron microscopy

Morphology of microparticle was examined by scanning electron microscopy. The view of the microspheres showed an irregular shape with a moderately smooth surface morphology.

Some of the microparticle showed a dented surface structure (fig 15),. The outer surface of the microparticle was dense and pores could be observed. The microparticle also showed some porous structure. It may be caused by the evaporation of solvent entrapped within the microspheres after forming a dense skin layer, but they showed good floating ability on the surface of the medium, indicating intact surface.

Micromeritic properties

The mean particle size of the floating microparticle formulation F1 to F6 containing ethyl cellulose using dichloromethane as solvent and formulation F7 to F12 containing ethyl cellulose using ethanol as solvent was in range of 266.07 to 317.84 µm and 270.49-325.27 µm respectively (as shown in table 15, 16). The mean particle size of the microparticle was found to increase with increasing ethyl cellulose concentration. The viscosity of the medium increases at a higher ethyl cellulose concentration. Shearing efficiency is also diminished at higher viscosities. This results in the formation of larger particles with greater ethyl cellulose concentration.

The bulk density, tapped density of formulation F1 to F6 containing ethyl cellulose using dichloromethane as solvent and formulation F7 to F12 containing ethyl cellulose using ethanol as solvent was in range of 0.441 to 0.610 gm/cm^3, 0.333 to 0.494 gm/cm^3 respectively, 0.486 to 0.0.714 gm/cm^3, 0.408 to 0.572 gm/cm^3 respectively, (as shown in table 17, 18).

The carr's index, Hausners ratio, angle of repose of formulation F1 to F6 containing ethyl cellulose using dichloromethane as solvent and formulation F7 to F12 containing ethyl cellulose using ethanol as solvent was in range of 9.05 to 14.57, 8.4 to 13.64 respectively, 1.10 to 1.22, 1.09 to 1.23 respectively, $29^0.32'$ to $37^0.40'$, $27^0.15'$ to $34^0.20'$ respectively (as shown in table 15, 16).Hausners ratio for all formulation was less than 1.25 indicate good flow. The flow properties are expressed in terms of carr's index. The carr's index for all formulation was less than 15. This indicates excellent flow compared to the original drug. The improvement in flow properties and suggests that the microparticles can be easily handled during processing.

Yield of floating microsphere

The percentage yield of floating microparticle formulation F1 to F6 containing ethyl cellulose using dichloromethane as solvent and formulation F7 to F12 containing ethyl cellulose using ethanol was in range of 92.73 to 97.82, 90.91 to 97.27 respectively (as shown in table 19, 20). To observe the effect of polymer concentration on the percentage yield of the floating microparticle, formulations were prepared at varying concentration of ethyl cellulose. The yield of the floating microparticle increased with increasing polymer concentration. At low concentration of ethyl cellulose polymer solution aggregated in a fibrous structure, as it solidified prior to forming droplets or the transient droplets were broken before solidification was complete due to poor mechanical strength resulting into low yield.

In-vitro buoyancy

The purpose of preparing floating microparticle is to extend the gastric residence time of a drug. The buoyancy test was carried out to investigate the floatability of the prepared microspheres. The microparticles were spread over the surface of a simulated gastric fluid and the fraction of microspheres buoyant and settled down as a function of time was quantitated. The in-vitro buoyancy of formulation F1 to F6 containing ethyl cellulose using dichloromethane as solvent and formulation F7 to F12 containing ethyl cellulose using ethanol as solvent was range from 70.34 to 92.12 %, 69.86 to 91.87 % respectively (as shown in table 21, 22). Among all formulation F6 was found to possess highest invitro buoyancy 92.12%. The results also showed a tendency that the larger the particle size, the longer floating time.

Incorporation efficiency

The drug Incorporporation efficiency of formulation F1 to F6 containing ethyl cellulose using dichloromethane as solvent and formulation F7 to F12 containing ethyl cellulose using ethanol as solvent was in range of 91.22 to 96.87, 89.98 to 96.54 respectively (as shown in table 23, 24). Results demonstrated that increase in concentration of ethyl cellulose, increased the entrapment of the drug. The drug entrapment efficiency was found to be good in all the formulation.

Crushing strength

The compressive strength or crushing strength of granules has been investigated by placing individual granules between platens and breaking them by application of a compressive load. In many formulations, there is an optimum range of average granule crushing strength for a given granule size. Granule strengths below the lower limit of this range may consolidate well, but tend to break down during mixing, handling and precompression, to generate fines which retard uniform die filling[59].

Crushing strength of Clarithromycin from floating microspheres were performed using T.A.X.T plus Texture Analyser. Crushing strength of formulation F1 to F6 containing ethyl cellulose using dichloromethane as solvent and formulation F7 to F12 containing ethyl cellulose using ethanol as solvent was in range of 50.579 to 101.987 N, 5.814 to 109.069 N respectively (as shown in table 21, 22). Results demonstrated that increase in concentration of ethyl cellulose, increased crushing strength of the microparticle (fig 30, 31).

In-vitro drug release

In-vitro drug release studies of Clarithromycin from floating microparticle were performed in 0.1N HCl for 3 hr using USP type 2 dissolution test apparatus. It was found that invitro drug release of formulation F1 to F6 containing ethyl cellulose using dichloromethane as solvent and formulation F7 to F12 containing ethyl cellulose using ethanol as solvent as follows

F1, F3, F4, F5, F6 show percentage drug release 47.25 to 97.79 % at end of 3 hour. Formulation F2 show percent drug release 98.07 % at end of 3 hr. While F7, F9, F10, F11, F12 show percentage drug release 48.65 to 84.17 % at end of 3 hour (as shown in table 26-37) and formulation F8 show percent drug release 94.02 % at end of 3 hr. Among all

formulations, F2 was found to be the best formulation as it release Clarithromycin 98.07 % in a sustained manner with constant fashion over extended period of time.

It was observed as the concentration of ethyl cellulose was increased percent release of Clarithromycin decreases. The increase in ethyl cellulose concentration leads to the increased density of polymer matrix into the microparticle which results in an increased diffusional pathlength. This may decrease the overall drug release from polymer matrix. Furthermore smaller microparticles are formed at lower polymer concentration and have larger surface area exposed to dissolution medium.

Drug release kinetics

The release mechanism of Clarithromycin from various formulations was determined by comparing their respective correlation coefficient. It shows that the results pattern of Clarithromycin microparticle corresponded best Hixson Crowell model, which shows a linear relationship between the percent drug remaining to be released Vs Time (as shown in fig 46).

SUMMARY AND CONCLUSIONS

Floating microparticles have a bulk density less than gastric fluids and thus it remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. Also floating microparticle provides a constant and prolonged therapeutic effect which will reduce dosing frequency.

In the present study, floating microparticle of Clarithromycin was prepared using polymer like ethyl cellulose by using ethyl cellulose as matrix materials and colloidal silicon dioxide (Aerosil) was used as the porous materials.

The objective of the study is presented in chapter 3. Initially, an extensive literature survey was done for the collection of theoretical and technical data. The review of literature, drug profile and excipient profiles are presented in chapter 4. This was followed by procurement and characterization of raw materials used in the study.

The surface morphology of the prepared floating microparticle was studied using scanning electron microscopy. The prepared floating microparticles also characterized by FTIR spectroscopy to find out any chemical interaction between Clarithromycin and polymers used. The prepared floating microparticles were evaluated for particle size, percentage yield, drug incorporation efficiency, micromeritic properties (like bulk density, tapped density, hausners ratio, angle of repose, compressibility index), in-vitro buoyancy, in-vitro drug release study, crushing strength and as described in chapter 5. The results indicated that the significant effect was observed of increased polymer concentration, on said parameters in each case. The details of results are given in chapter 6. The mean particle size of the microparticles significantly increased with increase in polymer concentration. Micromeritic study suggested excellent flow properties of prepared microspheres. The invitro release was in the following order F2>F3>F5>F4>F6>F1 & F8>F9>F10>F11>F7>F12.

The results of the present study on " Development and evaluation of floating microparticle of Clarithromycin" reveals following conclusions:

- Floating microparticles of Clarithromycin can be successfully prepared by using ethyl cellulose as matrix material and colloidal silicon dioxide (Aerosil) as the porous material.
- The percent yield of all floating microparticle formulation was more than 90% suggesting that the methods used for drug entrapment was effective. The percent yield was significantly increased as the amount of polymer was increased in each preparation method.
- The Incorporation efficiency was good in all the cases which suggested that optimized parameters were used in the method of preparations.
- The in-vitro buoyancy was more than 70 % after 4 hours indicated satisfactory performance of proposed formulations. The percent buoyancy increased significantly as the amount of polymer was increased in each preparation method.
- The mean particle size of microparticles was in the range of 266.07-325.27µm depending upon the concentration of polymer used. The particle size increased significantly as the amount of polymer increased.
- The flow properties of all the prepared microparticles were good as indicated by low angle of repose ($\theta < 40^0$) and low compressibility index . The good flow properties suggested that the microparticle produced were non-aggregated.
- The crushing strength of microparticle was in the range of 5.814-109.069 N depending upon the concentration of polymer used. The crushing strength increased the amount of polymer was increased in each preparation method.
- In-vitro release of floating microparticle of Clarithromycin was found to be in following order F2>F3>F5>F4>F6>F1 & F8>F9>F10>F11>F7>F12. Among all formulations, F2 was found to be the best formulation as it release Clarithromycin 98.07 % in a sustained manner with constant fashion overextended period of time.

Hence, finally it was concluded that the prepared Floating microparticle of Clarithromycin may prove to be potential candidate for safe and effective sustained drug delivery over an extended period of time.

BIBLOGRAPHY

1. Chien YW. Concepts and system design for rate controlled drug delivery in novel drug delivery system. 2nd ed,Newyork: Marcel dekker Inc.1992; 50;1-42.
2. Chiao CS, Robinson JR.Sustained release drug delivery system. In: Longer MA, Robinson JR (editors) Remington: The science and practice of industrial pharmacy. 19th edn. Eastern Pennsylvania. Mack publication company 1995;2:1660-75.
3. Gapa P, Gaba M, Garg R, Gupta GD. Floating microspheres: a review 2008;6(5). Available from URL:http://www.pharmainfo.net/reviews, floating microspheres –review.
4. Lalla JK.Introduction to controlled release and oral controlled drug delivery systems. The eastern pharmacist 1991;45:25-8.
5. R Garg,GD Gupta. Progress in controlled Gastroretentive Delivery systems. Trop J pharm Res 2008;7(3):1055-1066.
6. Orellana G, Isabel. Expert opinion on drug delivery 2005;2(3):419-33. Available online at www.Ingentaconnect.com.
7. Garg S, Sharma S. Gastroretentive drug delivery systems. Pharmatech 2004; 5(2):160-66.
8. Klausner EA, Lavy E, Friedman m, Hoffman A. Exandable Gastroretentive dosage forms.J.control. Rel. 2000; 63:235-59.
9. Shinde AJ, Harinath MN. Gastroretentive Drug delivery system :An Overview 2008;6(1)Available from URL http://www.pharmainfo.net/reviews/gastroretentive drug delivery system overview.
10. Tortora GJ,Grabowski SR. Principles of Anatomy and physiology. 10th edn, New York: John wiley and sons 2002; 866-73.
11. Ross & Wilson. Anatomy and physiology in health and illness , 9th edn, London : Churchill livingstone 1996;294-8.
12. Gadad AP, Naduvinamani SN, patil MB, Dandagi PM, Manvi FM. Floating alginate beads: A Novel approach to prolong gastric residence, an overview. Int.J pharma Excip 2008; 7(1):5-11.
13. Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics a treatise. 1st ed. vallabh prakashan. 2002; 337.
14. Patel GM, Patel HR, Patel M. Floating drug delivery system: An Innovative Approach to prolong gastric retension. Pharmainfo.net 2007; 5(6). Available from URL: http://www.pharmainfo.net/reviews/floating drug delivery system innovative approach prolong gastric retension.
15. Arora S, Ali j, Ahuja A, Khar RK, Baboota S . Floating drug delivery system: A review . AAPS pharm sci tech 2005; 6(3): E372-E390.

16. Davis SS. Formulation strategies for absorption windows. Drug dev Tech 2005; 10(4): 249-57.
17. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retension of drugs: A review. Research j pharm. And Tech. 2008; 1(4): 343-348.
18. Singh BN, Kim KH.Floating drug delivery system. An approach to oral controlled drug delivery via gastric retension. J control release 2000; 63; 235-59.
19. Shirwalkar AA, kumar SMR and Jacobs. Recent developments in Floating drug delivery systems for gastric retension of drugs. An overview Indian drug 2006; 43(9): 697-704.
20. JM patil, RS Hirlekar ,PS Gide ,VJ Kadam. Trends in Floating drug delivery system. Journal of scientific and industrial research 2006; 65: 11-21.
21. Shah S.H, patel J.K, Patel N.V. Stomach specific floating drug delivery system : A review Int J.pharm Tech res.2009, 1(3):623-33.
22. Deshpande AA, shah NH,Rhoders CT, malick w. Development of a novel controlled release system for gastric retension. Pharm.Res.1997; 14(6):815-9.
23. Nayak.A, Maji R, Das B. Gasteroretentive drug delivery system: a review. Asian journal of pharmaceutical and clinical research 2010; 3(1):1-10.
24. Arora S, Ali J, Ahuja A, khar RK, Baboota S. Floating drug delivery system: A review AAPS pharm sci tech 2005; 6:372-90.
25. Aejaz A, Development and characterization of floating microspheres of clarithromycin as gastroretentive dosage form IRJ P 2013,4(1) P.166-168.
26. Sato Y, Kawashima Y, Takeuchi H, Yamamoto H. *Invitro* and *invivo* evaluation of riboflavin containing microballoons for a floating controlled drug delivery system in healthy humans. Int J pharm. 2004; 275 (12): 97-107.
27. Lee JH, Park TG, Lee YB, Shin SC, Choi HK. Effect of adding non-volatile oil as a core material for the floating microspheres prepared by emulsion solvent diffusion method. J microencapsulation 2001; 18(1):65-75.
28. Streubel A, Siepmann J, bodmeier R. Multiunit gastro retentive drug delivery system: A new preparation method for low density microparticles. J microencapsulation 2003; 20(3):329-347.
29. Sunil k. Jain, A.M. Awasthi, N.K.Jain, G.P. Agrawal. Calcium silicate based microspheres of repaglinide for gastro retentive floating drug delivery: Preparation and *invitro* characterization. J controlled release 2005; 107:300-309.
30. Baboota S. Floating drug delivery system: A review. AAPS pharm sci Tech 2005; 6(3):E372-E389.
31. Kate V, Anantha Krishnan N. Treatment of Helicobacter pylori infection- A review. Indian Journal of pharmacology.2001; 33:410-416.
32. Yasunori sato, yoshiaki kawashimab, hirofumi takeuchib, hiromitsu yamamoto. *Invitro* evaluation of floating and drug releasing behaviours of hollow microspheres

(microballons) prepared by the emulsion solvent diffusion method. European journal of pharmaceutics and Biopharmaceutics 2004; 57:235-243.

33. Rajinikanth PS, Karunagaran LN, Balasubramaniam J, Mishra B. Formulation and evaluation of Clarithromycin microspheres for eradication of helicobacter pylori chem. Pharm Bull.2008;56(12):1658-64.
34. Patel A, Ray S, Thakur RS. *Invitro* evaluation and optimization of controlled release floating delivery system of metformin hydrochloride. DARU 2006; 55:277-285.
35. Kumaresh SS, Anandrao RK, Tejraj MA. Development of hollow microspheres as floating controlled release systems for cardiovascular drugs: Preparation and release characteristics. Drug development and Industrial pharmacy 2001; 27(6):507-515.
36. Shah SH, Patel JK, Patel N. Stomach specific floating drug delivery system: a review. International journal of pharmTech Research 2009 july-sept: 623-633.
37. Ramesh RP, Mahesh CP. Pharmaceutical formulation and development of floating and swellable sustained drug delivery systems: a review. E. Journal of science and Technology 2009; 4(2):1-12.
38. Ashish Gupta, Mona Nagar and Praveen Sharma. Formulation and evaluation of repaglinide microspheres.International journal of pharmacy and life sciences.2012; 3 (2):1437-1440.
39. Shraddha S. Badve, Praveen sher, Aruna Korde, Atmaram P. Pawar. Development of hollow or porous calcium pectinate beads for floating-pulsatile drug delivery. European journal of pharmaceutics and Biopharmaceutics. 2007; 65:85-93.
40. Vishal G.Karkhile, Dr. Ritesh R, Karmarkar, Manish A. Formulation and evaluation of floating tablets of furosemide. International journal of pharma. Research & development (IJPRD) 2009; 12 (1):1-9.
41. A.H. El-Kamel, M.S. Soakar, S.S. Al Gamal, V.F. Naggar. Preparation and evaluation of ketoprofen floating oral delivery system. International journal of pharmaceutics.2001; 220:13-21.
42. Yogesh Garg, Kamla pathak. Design and *Invitro* performance evaluation of purified microparticles of Pravastatin sodium for intestinal delivery. AAPS pharm Sci Tech.2011; 12 (2):673-682.
43. N.V. Satheesh Madhav, Shivani kala. Review on microparticulate drug delivery system. International journal of pharmTech research.2011; 3 (3): 1242-1254.
44. Aulton ME. Pharmaceutics. The science of dosage form design.2nd ed.Livingstone C.Elsevier science Ltd. 2002; 9:324-8.
45. S.K.Senthilkumar, B. Jaykar, S.Kavimani. Formation and characterization and invitro evaluation of floating microspheres of Rabeprazole sodium; JITPS; 2010; vol.1 (6):274-282.

46. M.Najmuddin, Aejaz Ahmed, Sachin shelar, V.Patel, T. Khan;Floating microspheres of the ketoprofen, International journal of pharmacy and pharmaceutical sciences2010;vol (2):164-168.
47. Lansoprazole Med Lett Drugs Ther 1995 july 21; 37(953):63-64.
48. Jianhu LIU, Rong yang, Lulu jing. Synthesis and characterization of novel buoyant phytocatalyst; Nano science 2006;6: 126-130.
49. Hemangi S patil, Moreshwar patil, Bharat T kade. Formulation and *invitro* evaluation of floating microsphere of Acyclovir. Arch pharm sci.research. 2009;(1):194-199.
50. Nicole kavangh, Owen I, Corrigan. Swelling and erosion property of Hydroxypropylmethylcellulose matrices influence of agitation rate and dissolution medium composition. International journal of pharmaceutics.2004; (279): 141-152.
51. Philip Miner, Philip O.Kartz, Yusong chen. Gastric acid controlled with PPI's. American journal of gastroenterology 2003 (812); 2616-2620.
52. Sunil.K.Jain, Govind p, Agrawal. Evaluation and porous carrier based floating orlistate microsphere for gastric delivery. AAPS pharm-Sci.tech.2006 (7):125.
53. Rajesh Garg, GD Gupta. Gastro retentive floating microspheres of silymarin. Tropical journal of pharmaceutical research2010 (1); 59-66.
54. Hardman JG, Limbird LE. Godman and Gilmans 'The pharmacological basis of Therapeutics'. 10th ed. New York:McGraw Hill;2001.
55. Tripathi KD. Essentials of medical pharmacology, 4th ed. New delhi, Jaypee Brothers (p) Ltd; 1994.
56. Raymond CR. Handbook of pharmaceutical Excipients. 5th edition: Pharmaceutical Press: 2006.
57. Parasuram RR, Moidutty luqman. Chetan Hb. Preparation and evaluation of delayed release aceclofenac microspheres. Asian Journal of Pharmceutics.2008; oct-dec: 252-254.
58. Manavalan, Ramasamy, physical pharmaceutics, 2nd ed. India: Vignesh publisher.2004; 12(5):32-5.
59. Lachman L.Liberman HA. Kanig JL. The theory and practice of industrial pharmacy, Varghese Publishing House, Bombay.1991; 10(3):78.